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No. 08-___

IN THE

Supreme Court of the United States

MYLAN LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., & UDL LABORATORIES, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. & TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Does 35 U.S.C. § 285 permit the imposition of a ten-million-dollar attorney-fee award based substantially on (i) a generic drug maker's challenge to a patent's validity on different grounds than those stated in its pre-suit notice to the brand company, and (ii) the trial court's post-trial determination that the drug maker's initial (and ultimately unlitigated) theory lacked merit.

PARTIES TO THE PROCEEDINGS

Petitioners are Mylan Laboratories, Inc. (n/k/a Mylan Inc.), Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. Respondents, Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc. were the plaintiffs-appellees below. Alphapharm Pty. Ltd. and Genpharm, Inc., defendants-appellants below (now owned by Mylan Inc.), are not parties to this petition.

CORPORATE DISCLOSURE STATEMENT

Petitioner Mylan Laboratories, Inc. (n/k/a Mylan Inc.) has no parent corporations, and no publicly held company owns 10% or more of Mylan Inc.'s stock. Petitioners Mylan Pharmaceuticals, Inc. and UDL Laboratories, Inc. are wholly owned subsidiaries of Mylan Inc.

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PETITION FOR A WRIT OF CERTIORARI

Mylan Laboratories, Inc. (n/k/a Mylan Inc.), Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively "Mylan") respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit in this case.

OPINIONS BELOW

The opinion of the United States Court of Appeals for the Federal Circuit (Pet. App. 1a-25a) is reported at 549 F.3d 1381. The opinion of the United States District Court for the Southern District of New York (Pet. App. 61a-110a) deeming the case exceptional is reported at 459 F. Supp. 2d 227. The district court's

decision establishing the amount of the fee award (Pet. App. 27a-60a) is unreported. The district court's decision in favor of respondents on the merits (Pet. App. 111a-227a) is reported at 417 F. Supp. 2d 341. The Federal Circuit's summary affirmance of that opinion (Pet. App. 245a-246a) is unreported. The district court's decisions denying Mylan permission to change its invalidity theory (Pet. App. 242a-244a), and denying Mylan's motion to reconsider that decision (Pet. App. 228a-241a) are unreported.

JURISDICTION

The judgment of the U.S. Court of Appeals for the Federal Circuit was entered on December 8, 2008. A petition for rehearing *en banc* was denied on January 23, 2009. The Chief Justice extended the time within which to file a petition for a writ of certiorari to and including May 25, 2009. App. No. 08A882. Because May 25, 2009 is a federal legal holiday, under this Court's Rule 30 the last day to timely file this petition is the following day, May 26, 2009. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

RELEVANT STATUTORY AND REGULATORY PROVISIONS

35 U.S.C. § 285 provides: "The court in exceptional cases may award reasonable attorney fees to the prevailing party." The appendix to this brief reproduces the relevant portions of 21 U.S.C. § 355(j), 35 U.S.C. § 271(e), and 21 C.F.R. § 314.95. Pet. App. 247a-281a.

STATEMENT

Petitioner Mylan filed an abbreviated new drug application ("ANDA") for a drug patented by respondents, maintaining in its required pre-suit notice letter that the patent was invalid as obvious. Respondents then sued Mylan for patent infringement.

Based on disclosures during discovery, Mylan identified and pursued a different theory of invalidity. At trial, respondents prevailed. Deeming the case "exceptional," the district court awarded respondents more than $10 million in attorney fees from Mylan. The district court relied substantially on the fact that Mylan had not pursued the case on the theory of invalidity set forth in the initial pre-suit notice letter, which the district court deemed meritless. The Federal Circuit affirmed.

1. The Hatch-Waxman Act, 21 U.S.C. § 355 and 35 U.S.C. § 271(e), establishes the statutory scheme by which a generic manufacturer can apply to bring a drug to market when it believes that it can make and sell a generic version of the drug at substantially lower prices to those consumers who need it. Congress's purpose in enacting the relevant provisions of the Hatch-Waxman Act was to speed the development and entry into the market of generic equivalents of brand-name drugs, with the goal of "mak[ing] available more low cost generic drugs by establishing a generic drug approval procedure." H.R. Rep. No. 98-857, pt. 1 at 14 (1984).

To accomplish that goal, Hatch-Waxman created a process through which drug manufacturers can obtain FDA approval to market a generic version of an existing drug without replicating the expensive and time-consuming tests which proved that the brand-name drug was safe in the first place. *See In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 395 (S.D.N.Y. 2007). An ANDA allows a generic drug manufacturer to quickly demonstrate the safety and effectiveness of its proposed generic by showing that

the generic is "bioequivalent" to an already approved drug. *See generally* 21 U.S.C. § 355(j)(2).

In addition, the statutory scheme helps resolve the infringement and validity of any existing patent on the brand-name drug by allowing generic drug manufacturers to challenge the infringement and validity of patents covering brand-name drugs without actually marketing an accused infringing product and incurring the risk of potentially catastrophic patent infringement damages. *See* 35 U.S.C. § 271(e)(2), (e)(4)(c); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676-78 (1990) (describing the function of the ANDA process under the Hatch-Waxman Act). To challenge the drug patent's validity, however, the generic manufacturer must depend on publicly available information. Unless and until litigation ensues, the generic manufacturer cannot conduct discovery or obtain non-public documentation to support its pre-suit notice letter with, for example, the patent holder's internal documents and other relevant information bearing on the invalidity and enforceability of the patent.

2. Petitioner Mylan Pharmaceuticals, Inc. manufactures quality, lower-priced generic drugs. This petition arises out of Mylan's attempt to bring to market a generic version of a leading anti-diabetic drug, pioglitazone. Currently sold under the brand name Actos by Takeda Chemical Industries, Ltd., pioglitazone is one of a few drugs available in a class of diabetes treatments called thiazolidinediones ("TZDs"). *See* Pet. App. 119a-120a. Diabetics who require TZDs

to treat their disease generally pay between $164 and $241 per month for Actos.[1]

In July 2003, Mylan and three other generic drug manufacturers filed ANDAs seeking to market a generic version of pioglitazone. In its ANDA, as required by statute, Mylan stated that, in its opinion and to the best of its knowledge, Takeda's patent on pioglitazone was invalid—a so-called Paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV"). A Paragraph IV certification is a "highly artificial act of infringement" that, by conferring a right on the patent holder to bring a suit for technical infringement before the competing product is brought to market, "enable[s] the judicial adjudication" of the patent's infringement and validity. *Eli Lilly & Co.*, 496 U.S. at 678. Paragraph IV thus is designed to spare generic drug manufacturers the prospect of crippling money judgments that would arise if they entered the market before the patent's validity was resolved and that would deter the marketing of needed lower-priced generic drugs.

When a generic manufacturer's ANDA invokes Paragraph IV, the manufacturer is required by law to set forth a statement of the reasons it believes, based on the limited information available at that time, that the patent is invalid. Here, Mylan asserted that the Takeda patent was obvious. A patent is invalid due to obviousness if "the differences between the subject matter sought to be patented and the prior

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[1] Consumers Union of the U.S., *Consumer Reports Best Buy Drugs: Treating Type 2 Diabetes: The Oral Diabetes Drugs: Comparing Effectiveness, Safety, and Price* 22 (2009).

art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Mylan's pre-suit notice letter explained that the Takeda patent was invalid because it would have been obvious to one skilled in the relevant art, who would have been motivated to begin with one highly efficacious compound identified in the prior art and merely substitute a pyridine ring for the prior art's benzene ring, producing pioglitazone—with a reasonable expectation that the compound would work.

3. As specifically contemplated by Hatch-Waxman, Takeda responded by bringing this "damage-less" patent infringement suit against Mylan and one other ANDA filer (Alphapharm Pty., Ltd.). Mylan asserted the patent's invalidity as a defense. As the case proceeded, Mylan sought to modify its invalidity defense to reflect its discovery of previously unknown facts and test data known only to respondents. In particular, based on the evidence uncovered in discovery, Mylan developed a second theory of obviousness, in which it identified a different compound (compound 3894) in the prior art as the basis from which a person skilled in the art would arrive at pioglitazone. The only difference between the prior art compound and pioglitazone is the presence of an ethyl group (C_2H_5) in a particular location on the pioglitazone molecule's pyridine ring. Mylan posited that one skilled in the art would have thought it obvious, and would have been motivated, to add an ethyl group to the pyridine ring. But Mylan never had an opportunity to develop this theory at trial, because the district court forbade Mylan's use of an ob-

viousness theory other than the one stated in its Paragraph IV notice letter. Pet. App. 242a-244a, 228a-241a. Thus, the district court never heard any testimony on this theory at trial.

After completing discovery, Mylan elected to pursue a different theory of invalidity instead of obviousness. Mylan maintained that the Takeda patent was unenforceable due to Takeda's inequitable conduct in securing the patent from the U.S. Patent and Trademark Office ("PTO"). A patent is unenforceable if the patentee affirmatively misrepresented a material fact, failed to disclose material information, or submitted false information to the PTO with an intent to deceive. *See, e.g., Rentrop v. Spectranetics Corp.*, 550 F.3d 1112, 1119 (Fed. Cir. 2008). Mylan asserted that Takeda intentionally made material misrepresentations to the PTO in its comparison of six promising compounds in the patent, and that it omitted a relevant seventh compound entirely from the results. Mylan based this defense entirely on respondents' internal documents and other information obtained through discovery—information unavailable to Mylan before the suit.

Mylan advanced this unenforceability defense throughout the remainder of the proceedings in the district court, but Takeda eventually prevailed on the merits. *See* Pet. App. 227a. The court of appeals affirmed the district court's ruling without opinion. Pet. App. 26a.

After winning its infringement suit, Takeda sought attorney fees under 35 U.S.C. § 285, which allows a fee award in "exceptional" patent cases. Under settled precedent, a prevailing party must first demonstrate by clear and convincing evidence that

something exceptional about the case warrants the imposition of attorney fees. *Forest Labs., Inc. v. Abbott Labs.*, 339 F.3d 1324, 1327–28 (Fed. Cir. 2003) (internal citation omitted). The court then has discretion to determine whether, and in what amount, fees should be awarded to the prevailing party. *Id.* at 1328.

The district court deemed this case exceptional in substantial part because Mylan "attempt[ed] to substitute a new theory of obviousness following the close of fact discovery," which the court deemed "misconduct." Pet. App. 95a. The court also held that Mylan filed its ANDA in bad faith because the pre-suit notice letter that it sent to respondents after submission of the ANDA failed to state a "prima facie case of invalidity." Pet. App. 66a. The court further faulted Mylan's final inequitable conduct defense and various actions during the trial that the court also construed as misconduct. *See* Pet. App. 101a-107a.

The court awarded respondent a total of $16.8 million in attorney fees: more than $11.4 million from Mylan, with an additional $5.4 million from Mylan's co-defendants, Alphapharm and Genpharm. The award was the largest amount ever granted under Section 285 in Hatch-Waxman patent litigation.

4. The court of appeals affirmed. *See* Pet. App. 20a. The court of appeals held that the district court did not err in finding the case exceptional and upheld the large attorney-fee award. *Id.* at 14a-15a, 19a. The court viewed Mylan's Paragraph IV notice letter as baseless because discovery allegedly uncovered scientific errors in it, and adopted the district court's view that Mylan's inequitable conduct claim was "always frivolous." *Id.* at 15a-16a. Moreover, while the

panel majority found "the award of the total amount of a fee request . . . unusual," it refused to disturb the lower court's decision on attorney fees or the award of expert fees. *Id.* at 18a.

Judge Bryson concurred in the result, writing separately to question the district court's failure to observe the normally higher threshold of litigation misconduct required for an award of expert fees. *Id.* at 24a-25a.

Mylan's petition for rehearing en banc was denied. Pet. App. 245a-246a.

REASONS FOR GRANTING THE WRIT

The Federal Circuit has exclusive jurisdiction over attorney-fee awards in patent cases under 35 U.S.C. § 284. *See, e.g., Imagineering, Inc. v. Van Klassens, Inc.*, 53 F.3d 1260, 1263 (Fed. Cir. 1995). Thus, the court's decision upholding this massive fee award based on an improper legal standard for fees that confounds the purpose of the statutory regime established binding nationwide precedent that only this Court can correct.

THE FEDERAL CIRCUIT HAS ADOPTED AS BINDING NATIONAL PRECEDENT AN IMPROPER STANDARD FOR AWARDING ATTORNEY FEES UNDER THE HATCH-WAXMAN ACT

A. The Court Improperly Relied On The Modification Of Claims In Response To Discovery

1. The Federal Circuit upheld what is (to Mylan's knowledge) the largest attorney-fee award ever authorized under the Hatch-Waxman Act. This Court's

review is warranted because the Federal Circuit predicated its award on a legal standard that no other court of appeals applies to fee awards and that frustrates the very purpose of the Hatch-Waxman Act scheme.

The Federal Circuit upheld the award, which the district court assessed against Mylan on the ground that Mylan litigated a theory of patent invalidity that it had developed after discovery, rather than the pre-litigation legal theory it had advanced. Pet. App. 95a ("Mylan then engaged in further misconduct, attempting to substitute a new theory of obviousness following the close of fact discovery . . . . Mylan's misconduct was exceptional and deserves the imposition of sanctions."). That standard is legally untenable and has no counterpart in the law of other circuits administering attorney-fee statutes.

First, the federal court system's notice pleading and discovery system is specifically structured to allow and encourage parties to revisit and revise their initial claims for relief based upon discovery. Discovery under the Federal Rules is designed to help parties to "obtain the fullest possible knowledge of the issues and facts before trial." *Hickman v. Taylor*, 329 U.S. 495, 500-01 (1947). Moreover, the Federal Rules specifically contemplate a party's revision of its theory of the case in the wake of receiving discovery. *See, e.g.*, Fed. R. Civ. P. 15(a)(2) (instructing courts to "freely give leave [to amend pleadings] when justice so requires"); Fed. R. Civ. P. 15(b)(2) ("A party may move—at any time, even after judgment—to amend the pleadings to conform them to evidence and to raise an unpleaded issue."); *PAE Gov't Svcs., Inc. v. MPRI, Inc.*, 514 F.3d 856, 859 (9th Cir. 2007) ("Par-

ties usually abandon claims because . . . they have learned more about the available evidence and viable legal theories, and wish to shape their allegations to conform to these newly discovered realities. We do not call this sham pleading; we call it litigation."); *Winer Family Trust v. Queen*, 503 F.3d 319, 337 (3rd Cir. 2007) (noting that in proceedings against a corporation, the revelation of individual culpability through discovery is sufficient grounds to seek leave to amend the complaint to cover culpable individuals); *cf. Conley v. Gibson*, 355 U.S. 41, 47-48 (1957) (observing that simplified pleading is made possible by the availability of discovery to clarify issues later in the proceedings).

For that reason, courts generally encourage parties to revisit their pre-litigation positions based on information obtained through discovery and to abandon claims that have become untenable and add new claims that have surfaced or been bolstered by factual discovery. The Federal Circuit's standard, however, stands that practice on its head by holding that the decision to litigate based on a legal claim developed in light of discovery, rather than a pre-litigation position, constitutes conduct that can support an award of $10 million in attorney fees. The court did so without citing any support for that standard in the decisions of other courts of appeals administering attorney-fee statutes. Moreover, the court rested its fee determination on the conclusion that Mylan's pre-litigation position was lacking in merit and that the decision to litigate a claim that had insufficient merit to proceed to trial warranted sanction. That turns ordinary federal procedure on its head.

Second, the flaw in the Federal Circuit's approach is compounded by the fact that Mylan was *not* the plaintiff in this case; respondent was. The sanction here thus rests on Mylan's decision during litigation and post-discovery to pursue an affirmative defense that differed from a *pre-litigation* administrative position, which in turn was taken under a statutory scheme the very purpose of which is to liberalize challenges to patents by generic manufacturers. Congress understood that ANDA applicants would provide notice letters before litigation begins, without the benefit of any discovery and access to internal documents that can, and often do, lead to new defenses to an infringement claim.

Indeed, some patent defenses almost necessarily require discovery before they can be asserted. For example, inequitable conduct claims like that advanced by Mylan almost always reveal themselves after discovery because a patentee's misrepresentations or the withholding of material information are rarely matters of public record. The same can be true for on-sale bar defenses, by which an alleged infringer asserts the patent's invalidity based on the fact that the patented invention was on sale in the United States more than a year before a patent application was made. *See* 35 U.S.C. § 102(b); *Linear Tech. Corp. v. Micrel, Inc.*, 275 F.3d 1040, 1047 (Fed. Cir. 2001). If the patentee has made secret sales, the alleged infringer will need discovery to uncover them. And, of course, internal documents also can be relevant to some prior art defenses. A brand company's internal testing, for instance, can help refute or support a claim of unexpected results in an obviousness challenge. *See, e.g., McNeil-PPC, Inc. v. L. Perrigo*

Co., 207 F. Supp. 2d 356, 365-66 (E.D. Pa. 2002), *aff'd in relevant part*, 337 F.3d 1362 (Fed. Cir. 2003).

Indeed, prior to the Federal Circuit's ruling in this case, lower courts had held that a generic manufacturer does not act in bad faith when, upon receiving discovery, it forgoes its pre-suit defenses in favor of those that emerged during discovery. In *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, No. 04-754, 2007 WL 4300155 (D.N.J. Dec. 5, 2007), the district court held that the case was not appropriate for attorney fees even though Teva ultimately dropped every reference from its pre-suit notice letter. The court reasoned that reconsidering claims does not establish, by clear and convincing evidence, that the litigated claims were made in subjective bad faith.

Likewise, in *Merck & Co. v. Mylan Pharms., Inc.*, 79 F. Supp. 2d 552 (E.D. Pa. 2000), the court held that "it is far from unreasonable that a party to such a financially significant lawsuit would want to explore multiple theories of recovery and defense and engage in the discovery necessary to support these theories." *Id.* at 556. Such "good faith persistence cannot be deemed to constitute 'exceptional' behavior." *Ibid.*

In this case, as Mylan learned more about respondent's patent and its conduct, it elected not to pursue its initial theory of obviousness in favor of the argument that respondent had engaged in inequitable conduct—a claim that was sufficiently tenable to require resolution through trial and that Mylan thought was its best defense. Mylan accordingly had no cause to build a litigation record in support of its pre-litigation administrative claim, and no reason to defend that pre-litigation administrative claim at

trial. Yet, after Mylan lost at trial, the district court used its own assessment of the merits of Mylan's *unlitigated* theory as a basis for awarding attorney fees. That decision discourages the very review and refinement of claims that the discovery process promotes and forces parties to continue litigating potentially weaker claims just to avoid having them cited as a basis for fees.

3. The decision also confounds congressional purpose. In Hatch-Waxman, Congress designed a statutory scheme that depends on ANDA applicants' willingness to make initial claims of patent invalidity before obtaining discovery. Congress counter-balanced that incentive by creating a streamlined litigation procedure for patent holders to resolve the invalidity claims. Construing Section 285 to allow an inference of bad faith because an ANDA applicant properly changed positions based on discovery and instead litigated through trial a claim rooted in discovery evidence puts the administrative scheme and attorney-fee provision at cross-purposes. The decision also skews the balance Congress legislated, by giving patent holders all the benefits of streamlined litigation to protect their claims while erecting barriers to the pre-suit administrative assertion of claims by ANDA applicants.

There are, in fact, myriad examples of ANDA filers prevailing on theories put forth for the first time in litigation and, as a result, cheaper generic drugs reached the market as Congress desired and to the great benefit of consumers. *See Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955 (Fed. Cir. 2001) (fluoxitine/Prozac) (patent was invalidated based on a theory asserted for the first time during discovery);

SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312 (Fed. Cir. 2006) (paroxetine/Paxil) (successful invalidity defense developed during discovery); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007) (ramipril/Altace) (court of appeals held the patent invalid based on an obviousness defense developed for the first time in litigation); *Alza Corp. v. Mylan Laboratories, Inc.*, 464 F.3d 1286 (Fed. Cir. 2006) (oxybutynin/Ditropan XL) (prevailing on theory not contained in the ANDA notice); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362 (Fed. Cir. 2003) (loperamide/Imodium Advanced) (two patents invalidated based on theory developed post-discovery).

Four other cases involved other post-discovery defenses, such as non-infringement or inequitable conduct before the PTO. *See Ferring B.V. v. Barr Laboratories, Inc.*, 437 F.3d 1181 (Fed. Cir. 2006) (desmopressin/DDAVP); *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 176 F. App'x 117 (Fed. Cir. 2006) (enoxaparin/Lovenox); *Purdue Pharma L.P. v. Endo Pharmaceuticals, Inc.*, 438 F.3d 1123 (Fed. Cir. 2006) (oxycodone/OxyContin); and *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003) (gabapentin/Neurontin).

Those cases suggest that using the attorney-fee provision to deter and chill ANDA claims and to sanction the development of post-discovery claims will deprive the court of winning arguments of invalidity and so deprive the public of affordable life-saving and life-improving drugs.

To be sure, the court of appeals wrapped its holding in language indicating that it considered the claims to be "baseless." Pet. App. 15a. But the prob-

lem here is that the court of appeals rested its "baseless" label in significant part on the fact that Mylan had changed its pre-litigation administrative position and had formulated a new claim based on discovery. It is that critical aspect of the court's ruling that both contravenes established law and practice favoring such review and refinement of claims and derails Congress's statutory scheme encouraging pre-suit administrative claims of patent invalidity to ensure that generic equivalents get to market as often as possible.

B. The Court Adopted An Erroneous Standard For Assessing Bad Faith

The damage wrought by the court of appeals' decision is compounded by the threshold the court adopted for determining whether a Paragraph IV claim has been filed in bad faith. The court of appeals upheld, based on prior circuit precedent, *Yamanouchi Pharm. Co., Ltd v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1347 (Fed. Cir. 2000), the district court's conclusion that bad faith was established because the ANDA notice failed to state a "prima facie case of invalidity." Pet. App. 66a.

That legal standard lacks any basis in law. Indeed, this Court has held that a *complaint* need not establish a prima facie case to survive a motion to dismiss. *See Swierkiewicz v. Sorema, N.A.*, 534 U.S. 506, 511 (2002); *see also Bell Atlantic Corp. v. Twombly*, 127 S. Ct. 1955, 1965-66 (2007). Absolutely nothing in Hatch-Waxman supports the court's conclusion that the pre-litigation administrative ANDA filing and notice letter must meet a *higher* threshold than a complaint in civil litigation.

Quite the opposite, the *raison d'être* of the administrative scheme is to permit filings based on a more informal showing, and in exchange, protecting patent holders with a more informal route to defend their patents. To that end, the contents of the notice are prescribed by 21 U.S.C. § 355(j)(2)(B)(iv)(I)–(II). That provision mandates that the Paragraph IV notice letter set forth "the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." *Ibid.* The statute does not require the generic drug applicant to set forth facts that would make out a prima facie case of invalidity. Rather, the applicant's notice need only be sufficient to advise the patent holder of the generic manufacturer's assertion that the patent is invalid and thus to set the stage for litigation.

Once the case enters litigation the content of the pre-suit Paragraph IV notice is largely irrelevant. Nothing in the statute binds the applicant to the theories presented in the pre-suit notice; the ordinary rules of litigation apply, so the statutory scheme and rules of pleading in the federal courts thus provide that notice of an applicant's litigation theories comes from the answer to the complaint and any subsequent court filings. In short, the pre-suit Paragraph IV statement serves a limited notice function. Its principal purpose is to trigger the litigation, which is where the theories are developed and tested in full. Indeed, years often pass between the filing of the pre-suit notice and the trial—years in which discovery often produces the bases for new infringement defenses.

Furthermore, the principal purpose for deeming the ANDA filing to be an act of infringement is to

provide a "jurisdictional basis" for the litigation. *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1349 (Fed. Cir. 2004). As long as the ANDA applicant has complied with the filing requirements of the statute and presented colorable arguments, it has discharged Congress's purpose. The Federal Circuit rule, by contrast, imposes an exceptionally high pleading standard on an informal *pre-suit* administrative process and creates a substantial risk that, as occurred here, 20/20 hindsight will be used by courts to adjudicate the merits of an administrative pre-litigation claim years later at the *end* of litigation—pre-suit claims, as in this case, that were never litigated or otherwise tested at trial. That approach cannot be reconciled with statutory text or purpose, and carves the ANDA filing out for exceptional burdens that this Court has held may not even be imposed on civil litigants (such as the plaintiff's own complaint in this case).

C. The Unprecedented Size Of The Fee Award Merits Review Because It Will Chill The ANDA Process

The lower courts granted Takeda a fee award so massive that its counsel touts it as "the largest fee award ever in the history of ANDA litigation."[2] Given the rapidly rising costs of patent litigation, *see infra* n.3, the ruling below opens ANDA filers to ever-expanding downside risks in exchange for their undertaking the socially beneficial project of marketing

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[2] Biography of Andre K. Cizmarik, http://www.eapdlaw.com/professionals/detail.aspx?attorney=205 (last visited Mar. 30, 2009).

cheaper drugs. That exposure conflicts with the special litigation process Congress designed specifically to minimize and avoid the substantial financial deterrent that patent awards otherwise erect against the vital effort to bring generic products to market.

Moreover, the size of the disparity between *this* award and others suggests that the purpose of the award was as much to punish Mylan as to compensate Takeda. But compensation, not punishment, is the purpose of Section 285. *See Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337, 1347 (Fed. Cir. 2004) (observing that awards made pursuant to Section 285 are meant to be compensatory in nature). Indeed, Judge Bryson acknowledged in his partial concurrence that the district court's award had a punitive aspect. *See* Pet. App. 24a-25a (Bryson, J., concurring in part and concurring in the result in part). In addition to attorney fees, the district court awarded expert fees—a sanction, as Judge Bryson observed, that is both extraordinary and punitive. *Ibid.*

Congress enacted the ANDA filing process in general and the Paragraph IV certification process in particular to allow generic manufacturers to test the validity and enforceability of a patent without assuming a massive financial risk—the prospect of large money damages that attend a traditional infringement action. *See* H.R. Rep. No. 98-857, pt. 1 at 28 (opining on the value of the Hatch-Waxman created cause of action as a "remedy [that] permits the commencement of a legal action for patent infringement *before the generic drug maker has begun marketing* . . . fairly balances the rights of a patent owner . . . and the rights of third parties") (emphasis added).

The rulings below, however, open the door to punitive attorney-fee awards and thus create the very type of multi-million dollar monetary risk that Congress strove to avoid.[3] *See, e.g.*, Teva Pharm. Indus. Ltd., Annual Report (Form 20-F), at 6-7 (Feb. 27, 2009) (generic manufacturers' business is especially sensitive to litigation risks).

Congress did not intend Section 285 to be employed as a *post hoc* tool for punishing ANDA filers for invoking the informal administrative process that Congress designed specifically to encourage the testing of patents when a generic drug is available. The Federal Circuit's decision and the legal standards it adopted defy that purpose. Only this Court can put this program, which is a critically important aspect of reducing medical costs, back on track.

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[3] And the degree of risk is increasing as the costs of patent litigation increase: rapidly. *Compare* Am. Intellectual Prop. Law Ass'n, *Report of the Economic Survey* I-91 tbl.Q36f (2007) (showing an average cost of $5.499 million to litigate a patent worth over $25 million) *with* Am. Intellectual Prop. Law Ass'n, *Report of Economic Survey* 85 tbl.22 (2001) (showing an average cost of $2.992 million to litigate a patent worth over $25 million).

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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MAY 26, 2009

APPENDIX

(2)

Supreme Court, U.S.
FILED

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OFFICE OF THE CLERK

No. 08-

IN THE

Supreme Court of the United States

MYLAN LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., & UDL LABORATORIES, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. & TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

APPENDIX TO THE PETITION FOR A WRIT OF CERTIORARI

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United States Court of Appeals,
Federal Circuit.

TAKEDA CHEMICAL INDUSTRIES, LTD., and Takeda Pharmaceuticals North America, Inc., Plaintiffs-Appellees,

v.

MYLAN LABORATORIES, INC., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc., Defendants-Appellants,

and

Alphapharm Pty., Ltd. and Genpharm, Inc., Defendants-Appellants.

Nos. 2007-1269, 2007-1270.

Dec. 8, 2008.
Rehearing En Banc Denied Jan. 23, 2009.

Background: Patentee brought action against generic drug companies alleging infringement of patent directed toward chemical compound known as pioglitazone when defendants filed abbreviated new drug application (ANDA) to make generic form of pioglitazone. After entering judgment in patentee's favor, 2006 WL 618424, the United States District Court for the Southern District of New York, Denise L. Cote, J., 459 F.Supp.2d 227, found case to be exceptional and awarded attorney fees. Defendants appealed, and appeals were consolidated.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:

(1) district court did not commit clear error in finding that companies' filing of certifications with their ANDAs was in bad faith;

(2) district court did not abuse its discretion in

awarding attorney fees of $16,800,000; and
(3) district court did not abuse its discretion in awarding patentee its expert fees pursuant to its inherent powers.

Affirmed.

Bryson, Circuit Judge, concurred in part, concurring in result in part, and filed opinion.

David G. Conlin, Edward Angell Palmer & Dodge LLP, of Boston, MA, argued for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola and Andre K. Cizmarik, of New York, NY.

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Edgar H. Haug, Frommer Lawrence & Haug LLP, of New York, NY, argued for defendants-appellants Alphapharm Pty., Ltd., et al. With him on the brief were Kevin Murphy and Jeffrey A. Hovden.

Thomas C. Goldstein, Akin Gump Strauss Hauer & Feld LLP, of Washington, DC, argued for amicus curiae. With him on the brief was Christopher M. Egleson.

Before LOURIE, RADER, and BRYSON, Circuit Judges.

Opinion for the court filed by LOURIE, Circuit Judge.

Opinion concurring in part and concurring in the result in part filed by BRYSON, Circuit Judge.

LOURIE, Circuit Judge.

Alphapharm Pty. Ltd. and Genpharm, Inc. (collectively, "Alphapharm") and Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively, "Mylan") appeal from the final judgment of the United States District Court for the Southern District of New York. On September 20, 2006, the court granted a motion by plaintiff and patentee Takeda Chemical Industries, Ltd. and its affiliate Takeda Pharmaceuticals North America, Inc. (collectively, "Takeda") to find the case relating to Hatch-Waxman challenges made by Alphapharm and Mylan in connection with Takeda's U.S. Patent 4,687,777 ("the '777 patent") to be exceptional and to award attorney fees. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 459 F.Supp.2d 227 (S.D.N.Y.2006) (" September Opinion"). On March 21, 2007, the court quantified the attorney fees, expenses, and expert fees, awarding Takeda $11,400,000 from Mylan and $5,400,000 from Alphapharm, with interest. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, Nos. 03-8253, 04-1966, 2007 WL 840368 (S.D.N.Y. Mar. 21, 2007) (" March Opinion"). Because we conclude that the district court did not clearly err in finding that this was an exceptional case because of the misconduct of Mylan and Alphapharm and did not abuse its discretion in awarding attorney fees, we affirm.

BACKGROUND

The '777 patent covers the anti-diabetic drug pioglitazone, for which Takeda has enjoyed commercial

success under the name ACTOS®. Alphapharm and Mylan are two generic drug companies that sought approval to produce generic versions of pioglitazone under the Hatch-Waxman Act. That legislation provides the mechanism for a generic drug company to file an abbreviated new drug application ("ANDA"). An ANDA announces the intention of the filer to sell a bioequivalent form of a drug when approved by the FDA, and the filer makes a certification regarding existing patents covering the drug and its use. 21 U.S.C. § 355(j) (2006). Both Mylan and Alphapharm chose to make certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV"), certifying that the '777 patent was invalid for obviousness. In response, Takeda sued Alphapharm and Mylan for infringement.

At trial, Alphapharm and Mylan each changed the focus of their invalidity arguments from those in their certification letters. Alphapharm pointed to a compound referred to as compound b, which Takeda disclosed in U.S. Patent 4,287,200 ("the '200 patent") and in a 1982 scientific article[1] ("Sohda II"), as evidence that pioglitazone was structurally obvious at the time the invention was made. Mylan advanced an inequitable conduct argument based on alleged misrepresentations by Takeda to the Patent and Trademark Office ("PTO"). On February 21, 2006, after an extensive bench trial, the district court held the invention of the '777 patent to be nonobvious and enforceable. *Takeda Chem. Indus., Ltd. v. Mylan Labs.,*

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[1] T. Sohda et al., *Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl] thiazolidine-2, 4-dione (ADD-3878) and its Derivatives*, 30 Chem. Pharm. Bull. 3580 (1982).

Inc., 417 F.Supp.2d 341 (S.D.N.Y.2006). The district court entered final judgment on March 13, 2006, and we affirmed the district court in two separate appeals. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed.Cir.2007); *Takeda Chem. Indus., Ltd. v. Ranbaxy Labs., Ltd.*, No. 06-1364, 2007 U.S.App. LEXIS 15883 (Fed. Cir. June 28, 2007).

Takeda then moved for an award of attorney fees against both Mylan and Alphapharm on the theory that this was an exceptional case. When a patent has been infringed by the filing of an ANDA, 35 U.S.C. § 271(e)(4) provides for the grant of attorney fees under 35 U.S.C. § 285, which in turn allows the court to award reasonable attorney fees to a prevailing party in exceptional cases. Takeda contended that Mylan and Alphapharm each lacked a good faith basis for their Paragraph IV letters and engaged in misconduct throughout the litigation.

On September 20, 2006, the district court agreed with Takeda in an opinion that discussed the Paragraph IV letters and litigation conduct of Alphapharm and Mylan in the same thorough manner as the court's previous decision regarding the validity of the '777 patent. Regarding Alphapharm, the court held that the Paragraph IV certification letter was "so devoid of merit and so completely fail[ed] to establish a prima facie case of invalidity that it must be described as 'baseless.' " September Opinion, 459 F.Supp.2d at 235. The court discussed at length how Alphapharm's argument at trial focused on compound b as the lead compound for future research, whereas Alphapharm's certification letter focused on two other compounds

and contained scientific errors. The court also analyzed what it saw as Alphapharm's litigation misconduct, which mainly consisted of a shifting theory of obviousness that did not explain why compound b would have been identified as the lead compound. As a result, the court found that this was "the exceptional case where an examination of the totality of the circumstances amply justifies, indeed compels, the award of attorneys' fees." *Id.* at 245.

Similarly, the court held that Mylan's certification letter was filed in bad faith and with no reasonable basis to claim the '777 patent invalid. The court discussed how Mylan argued in its Paragraph IV letter that the invention of pioglitazone was obvious based on Takeda's disclosure of a compound in the ' 200 patent and Sohda II (referred to as compound 16 and compound 14, respectively) only to abandon this theory entirely during the litigation. In addition, the court discussed Takeda's numerous allegations of litigation misconduct committed by Mylan in its pursuit of an inequitable conduct claim, which principally addressed Takeda's representations to the PTO regarding a different compound disclosed in the prior art, compound 3894. The court also found that the inequitable conduct claim was "always frivolous" and unsupported, as Mylan did not present any evidence that Takeda hid or misrepresented any information to the PTO. *Id.* at 249. The court concluded that the totality of the circumstances, including other instances of Mylan's untimely conduct, justified the award of attorney fees against Mylan as well.

On March 21, 2007, the district court quantified the fees at $16,800,000, with Alphapharm to pay

$5,400,000 and Mylan, $11,400,000. In assessing the amount of the award, the court stated that the attorneys for Takeda did uniformly excellent work in a complex and contentious litigation. When allocating the attorney fees, the court accepted the division proposed by Takeda, with Mylan responsible for two-thirds of the total amount. The court also awarded Takeda its expert fees under its inherent power to impose sanctions, along with expenses and interest beginning on the date of the September Opinion.

Mylan and Alphapharm filed separate timely appeals from the district court's judgment. The appeals were consolidated on December 17, 2007. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Exceptional Case Finding

35 U.S.C. § 285 provides that a trial court "in exceptional cases may award reasonable attorney fees to the prevailing party." The decision to award attorney fees is within the discretion of the trial judge, but the conclusion that a case is exceptional is a finding of fact reviewable only for clear error. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed.Cir.1989). We address the arguments of the appellants with regard to the district court's finding of an exceptional case individually.

1. Alphapharm

On appeal, Alphapharm argues that its Paragraph IV letter was not baseless under structural obviousness

law. Alphapharm asserts that its certification letter made out a prima facie case of obviousness and that, contrary to what the district court held, Alphapharm was not required to explain why a skilled artisan would have identified compound b as the lead compound in its certification letter. As evidence of what it argues was a reasonable chance to succeed, Alphapharm points to Judge Dyk's concurrence in the prior decision of this court. Alphapharm also argues that the fact that its original theory did not prevail at trial falls far short of clear and convincing evidence required for the district court to find that its certification letter was baseless. Alphapharm further claims that affirming the district court's ruling would chill challenges by generic drug companies to otherwise invalid patents by requiring the inclusion of every possible theory of invalidity in a certification letter rather than allowing an ANDA filer to develop its theories during the course of discovery. Similarly, Alphapharm argues that the district court erred in finding litigation misconduct because Alphapharm consistently argued an obviousness theory and merely honed its arguments in response to documents produced during discovery by Takeda. Alphapharm also disagrees with the court's characterization of certain of its evidence as an attempt to inject an inequitable conduct argument into the obviousness inquiry.

Alphapharm and Mylan are supported in this appeal by amicus curiae, the Generic Pharmaceutical Association, who submitted a brief and was permitted to orally argue before the court. Amicus argues that failure to reverse the district court's finding of an exceptional case would deter generic applicants from presenting defenses at trial that were not included in

their certification letters. Amicus asserts that changing defenses is normal conduct during litigation, especially in patent cases, when ANDA applicants prepare certification letters without the benefit of discovery. As a result, amicus argues, ANDA filers should be allowed to litigate the best available theories at trial, regardless of their inclusion in certification letters. Amicus asserts that if the district court decision stands, it will have a chilling effect on future ANDA patent challenges.

Takeda responds that Alphapharm's argument, that it should benefit from a presumption of obviousness based on structural considerations, has already been rejected by this court. In addition, Takeda points out that Alphapharm's certification letter included scientific errors and that Judge Dyk's concurrence did not address the claim of the '777 patent specific to pioglitazone, the invalidity of which was necessary for Alphapharm's success. Finally, Takeda asserts that the record amply supports the district court's finding that Alphapharm presented constantly shifting, but always baseless, obviousness arguments. That finding, Takeda argues, supports the court's conclusion that Alphapharm's obviousness theories never had a good faith basis and thus warranted an exceptional case finding.

As noted by Takeda, we have already held that the district court did not commit reversible error by refusing to apply a presumption of motivation to select compound b as the lead compound based on structural obviousness. *See Takeda*, 492 F.3d at 1360. Accordingly, although Alphapharm made brief reference to compound b in its Paragraph IV letter, it failed to

provide any reason in its Paragraph IV letter to identify compound b as the lead compound and thus did not make out a prima facie case of obviousness based on the structural similarity between compound b and pioglitazone. Any support Alphapharm hopes to gain from Judge Dyk's concurrence is moreover lacking, as his opinion addressed the possible overbreadth of two claims in the ' 777 patent and not, as Alphapharm claims, structural obviousness based on the prior disclosure of compound b. *Id.* at 1364 (Dyk, J., concurring).

Furthermore, although it seems reasonable to expect assertions of invalidity based on prior art to remain relatively consistent as the prior art should be known when the certification of invalidity is made, we do not believe that the district court faulted Alphapharm simply for changing its obviousness argument at trial from the theory advanced in the Paragraph IV letter. Rather, the court methodically examined a number of shortcomings in Alphapharm's Paragraph IV letter, which were made obvious by Alphapharm's "constantly shifting set of arguments," that supported the finding that the certification was baseless. September Opinion, 459 F.Supp.2d at 236. The court noted the stark contrast between Alphapharm's focus on compound b as the lead compound at trial with its discussion in the certification letter of two other compounds disclosed in Sohda II and how, as a result, Alphapharm "did not grapple with the many impediments evident in Sohda II for choosing compound (b) as a lead compound." *Id.* The court also catalogued scientific errors in Alphapharm's certification letter that the court saw as "insidious" and as underscoring that Alphapharm "did not act with due care or in

good faith" in filing its certification. *Id.* at 237. The court found that other assertions in Alphapharm's Paragraph IV letter were baseless because of undisputed evidence of pioglitazone's superiority and that Alphapharm abandoned these arguments at trial because "they were unsupportable, not because Alphapharm made a tactical decision regarding which argument should be emphasized at trial." *Id.* at 238. The court concluded that the deficiencies in Alphapharm's Paragraph IV letter were "so glaring" that they highlighted that Alphapharm "acted in bad faith in filing its Paragraph IV certification." *Id.* at 239.

The court also discussed in depth what it saw as Alphapharm's litigation misconduct. The court traced the many iterations of Alphapharm's theory of obviousness and pointed to Alphapharm's "utter failure" to account for the identification of compound b as the lead compound as required under structural obviousness law. *Id.* at 241. The court reasoned that Alphapharm had over two years to develop its obviousness arguments in its Paragraph IV letter, and its failure to explain "why its Statement was so flawed and why its description of obviousness went through such a dramatic evolution" was "overwhelming" evidence of Alphapharm's bad faith. *Id.* at 243. Finally, the court discussed assertions made by Alphapharm that were unrelated to the obviousness claim and "created confusion, wasted valuable court time, and increased the burden of the litigation on the parties." *Id.* When considering the totality of the circumstances, the court stated bluntly, "This case was not close." *Id.* at 244. The court's conviction in its findings could hardly be clearer.

A number of different circumstances may support the finding of an exceptional case, including "vexatious or unjustified litigation" or "frivolous suit," of which there must be clear and convincing evidence. *Beckman,* 892 F.2d at 1551. Indeed, one of the purposes of § 285 is to prevent " 'gross injustice' when the accused infringer has litigated in bad faith." *Id.* at 1552. In *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.,* we stated that "[t]he joint operation of §§ 271(e) and 285 require the paragraph (2) infringer to display care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity.... The Hatch-Waxman Act thus imposes a duty of care on an ANDA certifier." 231 F.3d 1339, 1347 (Fed.Cir.2000). Alphapharm now argues that *Yamanouchi*'s "duty of care" language lays out a simple negligence standard. Alphapharm further contends that this standard conflicts with *Beckman,* which, Alphapharm argues, establishes the far higher threshold of gross negligence. Alphapharm is incorrect on both points.

In the first place, *Beckman* does not set out a gross negligence standard. In *Beckman,* we stated that § 285 prevents "gross injustice" where a party has demonstrated "bad faith and misconduct during litigation." *Beckman,* 892 F.2d at 1553. In addition, *Yamanouchi* does not establish a simple negligence standard, nor did the district court in this case apply such a standard. Although *Yamanouchi* states that ANDA applicants owe a duty of care under the Hatch-Waxman Act, it explained that applicants fail to meet this duty when they file "baseless" certifications. 231 F.3d at 1347. Thus, *Yamanouchi* does not

stand for the proposition that ANDA applicants who are merely negligent can trigger § 285.

In this case, the district court correctly found that Alphapharm's filing would amount to litigation misconduct supporting an exceptional case finding if it were "baseless" and if it "fail[ed] to present even a prima facie case of invalidity in filing the paragraph IV certification." September Opinion, 459 F.Supp.2d at 232. Thus, the trial court did not apply a simple negligence standard but found Alphapharm's filing "baseless." Moreover, the trial court found misconduct during litigation. Given the district court's familiarity with the parties and the issues and its thorough discussion of Alphapharm's certification letter and litigation strategy, we cannot say that the court committed clear error in finding that this was an exceptional case due in part to the misconduct of Alphapharm. *See Beckman,* 892 F.2d at 1552 & n. 1 (noting that the district judge was in "the best position" to monitor litigation strategy and find bad faith).

2. Mylan

On appeal, Mylan argues that the district court based its finding of an exceptional case against Mylan on conjecture rather than requiring Takeda to show clear and convincing evidence. As support for its position, Mylan points to its decision not to pursue the same arguments at trial as in its Paragraph IV letter, arguing that because Mylan's original invalidity theory was never pursued, the court had to rely on speculation in finding the certification letter baseless. Mylan also asserts that its decision to amend its de-

fenses to include a revised obviousness claim and an inequitable conduct claim did not constitute litigation misconduct or demonstrate bad faith because it is customary to develop defenses during discovery. Mylan argues that the fact that it ultimately did not win on these claims does not render this case exceptional. Furthermore, Mylan asserts that the district court's decision to allow Mylan to assert its inequitable conduct claim demonstrates that it was not frivolous and thus was not litigation misconduct.

Takeda responds by pointing to the district court's analysis of the evidence regarding Mylan's certification letter and litigation misconduct. Takeda notes Mylan's error in characterizing compound 14 and pioglitazone as bioisosteres in its Paragraph IV letter, which certified that pioglitazone was obvious based on the disclosure of compound 14 in the '200 patent and Sohda II. Takeda argues that this invalidity argument was so devoid of merit that Mylan did not pursue this obviousness claim in discovery and abandoned it before trial. Takeda then argues that Mylan suddenly asserted a revised obviousness theory centering on compound 3894 that was similarly fraught with scientific errors. With regard to Mylan's inequitable conduct claim, Takeda asserts that this claim was also frivolous, as Mylan completely failed to present any evidence of intent to deceive the PTO, and notes that the court specifically stated that allowing Mylan to amend its defenses to include inequitable conduct did not mean that the amendment was timely or meritorious.

We conclude that the court did not commit clear error in finding that Mylan's misconduct contributed to

this being an exceptional case. In fact, Mylan's invalidity argument in its certification letter appears even more baseless than Alphapharm's. Mylan certified that pioglitazone was rendered obvious because Takeda had already disclosed compound 14, which had high efficacy, and simply replaced its benzene ring with a pyridine ring, which it described as a bioisostere, to create pioglitazone. But Mylan's Rule 30(b)(6) designee testified that no reason existed to choose compound 14 as the lead compound; Takeda's expert emphatically disagreed with the assertion that benzene and pyridine rings are bioisosteres; and Alphapharm's expert testified that the properties of compound 14 taught nothing with respect to pyridines. We find it unsurprising, therefore, that the district court characterized Mylan's defense of the merits of its Paragraph IV letter as "utterly frivolous." September Opinion, 459 F.Supp.2d at 247. In light of the scientific errors present in Mylan's certification letter, the fact that the court was unmoved by Mylan's decision not to pursue this obviousness claim at trial can hardly be deemed clear error. We believe the court had ample reason to hold that Mylan's certification letter was filed in bad faith and with no reasonable basis to claim the '777 patent invalid.

Similarly, the finding that Mylan engaged in litigation misconduct was well-supported and explained by the district court. The court deemed Mylan's later argument based on compound 3894 to be "extremely misleading." *Id.* at 247. In addition, the court discussed Takeda's seven asserted separate grounds for litigation misconduct committed by Mylan in its pursuit of an inequitable conduct claim. As Takeda points out, the district court stated that "its decision

to allow Mylan to bring its claim of inequitable conduct was absolutely not a finding that it was timely or meritorious." *Id.* at 249. Accordingly, the court found that the inequitable conduct claim was "always frivolous" and unsupported, as Mylan did not present any evidence that Takeda hid or misrepresented any information to the PTO. *Id.* We do not find persuasive Mylan's argument that the district court took issue with the mere fact that Mylan changed its theory of invalidity and then lost. Rather, the court determined that Mylan's initial certification letter was completely baseless and that the claims Mylan offered as substitutes were similarly frivolous. In short, the district court, which was in the best position to evaluate the entire strategy pursued by Mylan, did not commit clear error in finding litigation misconduct.

Finally, we find the "chilling" argument regarding ANDA filers advanced by Alphapharm and Mylan to be unpersuasive, despite the support provided by the amicus filing of the Generic Pharmaceutical Association. In making a Paragraph IV certification, appellants are statutorily required to "include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid." 21 U.S.C. § 355(j)(2)(B)(iv)(II) (2006). It is clear from the district court's opinion that it was not faulting Alphapharm or Mylan for the act of filing an ANDA that challenged the pioglitazone patent, nor did it limit the filers to the theories raised in their certification letters. Rather, the district court found the case exceptional based on the specific circumstances involved in this case, *viz.*, baseless certification letters compounded with litigation misconduct. In fact, the court addressed the deterrence argument directly:

There is no basis to find that this award of fees will deter ANDA filings and litigation. This award addresses baseless ANDA filings and the pursuit of frivolous ANDA litigation in bad faith and other litigation misconduct. The Hatch-Waxman Act cannot be read to immunize such conduct.

September Opinion, 459 F.Supp.2d at 251. Given the court's specific articulation that its ruling was directed toward baseless ANDA filings and litigation in bad faith, we decline to disturb the court's finding of an exceptional case as potentially chilling non-frivolous ANDA filings under the Hatch-Waxman Act. Well-supported filings challenging the validity and infringement of patents owned by an NDA holder should not raise the specter of an unjustified holding of an exceptional case.

B. Amount of Award

If a district court has not clearly erred in finding a case exceptional, we review the award of attorney fees for an abuse of discretion. *Yamanouchi*, 231 F.3d at 1346. The abuse of discretion standard also applies to the district court's exercise of its inherent power to award sanctions. *Amsted Indus. Inc. v. Buckeye Steel Castings Co.*, 23 F.3d 374, 379 (Fed.Cir.1994). Under that standard, we will affirm a district court unless its decision was "clearly unreasonable, arbitrary or fanciful, or based on an erroneous conclusion of law or fact." *Yamanouchi*, 231 F.3d at 1346.

Appellants argue that Takeda's award request was excessive for a litigation that lasted just two years

and culminated in a nine-day trial. They point to Takeda's billing entries and expenses as excessive and inadequately supported in arguing that the district court abused its discretion by not reducing the award from the requested amount. Mylan also argues that the court abused its discretion in failing to consider opinions of Mylan's experts regarding the reasonableness of the award and that the court had no basis for its two-thirds allocation of the fee award to Mylan. Finally, both Alphapharm and Mylan assert that the additional sanctions of expert fees and expenses were unjustified because there was no evidence of fraud or abuse of the judicial process.

Takeda responds that the district court examined all relevant factors in determining the amount of attorney fees, including the time entries and staffing of the litigation. Takeda also points to the court's analysis of Mylan's expert declarations and its reasoning for the allocation of the award in asserting that both decisions fell within the court's discretion. With regard to the expert fees, Takeda argues that the court had the discretion to impose a sanction because of the appellants' bad faith and vexatious conduct during the litigation.

Although the award of the total amount of a fee request is unusual, we have stated that such an award may be imposed and affirmed. *See Beckman*, 892 F.2d at 1553 ("[W]e can certainly imagine a case in which litigation misconduct would justify an award of attorney fees for the entire litigation."). That determination lies within the discretion of the trial judge, "who is in the best position to know how severely [a party's] misconduct has affected the litigation." *Id.*

Here, the district court left no doubt as to its opinion of the litigation and work performed by counsel. The court characterized the work of Takeda's counsel as "uniformly excellent" and determined that the attorney fee award was reasonable. March Opinion, 2007 WL 840368, at *4. Indeed, the court indicated that an even higher award would have been justified. The court found that none of the attacks on the size of the fee award had merit, and the court also gave specific reasons for disregarding Mylan's purported expert opinions, including a lack of experience on the part of the declarants with both the present litigation and patent litigation as a whole. Furthermore, the court explained its allocation of two-thirds of the fee burden to Mylan because it acted as lead defense counsel for discovery of the obviousness claims and then added considerably to the complexity of the case with an untimely assertion of an inequitable conduct claim. Given the court's reasoned analysis and familiarity with the litigation, we do not believe that the court abused its discretion with its award of attorney fees and related expenses. *See Mathis v. Spears*, 857 F.2d 749, 759 (Fed.Cir.1988) (allowing for the award of expenses under § 285).

As for the award of expert fees, a district court may invoke its inherent power to impose sanctions in the form of reasonable expert fees in excess of what is provided for by statute. *See Chambers v. NASCO, Inc.*, 501 U.S. 32, 50, 111 S.Ct. 2123, 115 L.Ed.2d 27 (1991); *Mathis*, 857 F.2d at 759 (noting that "full expert witness fees have been awarded, without specific statutory authorization, upon a finding of bad faith"). The use of this inherent power is reserved for cases with "a finding of fraud or abuse of the judicial proc-

ess." *Amsted*, 23 F.3d at 378. While it is true that the appellants' conduct did not amount to fraud, courts may use sanctions in cases involving bad faith that cannot be otherwise reached by rules or statutes. *See Chambers*, 501 U.S. at 46, 111 S.Ct. 2123 (discussing cases). Here, the court below could not award expert fees under § 285, but it was entitled to use its inherent powers to award Takeda the expert fees. Because of the court's numerous articulations of appellants' bad faith and vexatious litigation conduct, we cannot say that the decision to do so was an abuse of discretion.

We have considered the other arguments raised by appellants and find them unpersuasive.

CONCLUSION

Accordingly, we affirm the district court's finding of an exceptional case and the award to Takeda of $16,800,000 for attorney fees, expenses, and expert fees, plus interest.

AFFIRMED

BRYSON, Circuit Judge, concurring in part and concurring in the result in part.

I agree that the district court did not abuse its discretion in awarding Takeda attorney fees. As a practical matter, the task of determining whether a case is "exceptional" within the meaning of 35 U.S.C. § 285 so as to justify an award of attorney fees is necessarily committed almost entirely to the judgment of the district court. A district judge who has lived with a case and the lawyers for an extended period (four years in this case) is infinitely better situated than we are to make the kind of holistic judgments about the parties' conduct of the litigation that are required to assess whether the case should be treated as exceptional and whether fees should be awarded. Where the trial court applies the proper legal standards and conducts a thorough review of the circumstances bearing upon the section 285 inquiry, there is little room for a reviewing court to second-guess the trial court's judgment. In this case, the trial judge's analysis was thorough and her finding that the case was exceptional was not based on the application of an erroneous legal standard. Under these circumstances, I agree with my colleagues that we cannot overturn the court's judgment as to the applicability of sanctions under section 285.

With respect to the portion of the award attributable to expert witness fees, I would uphold the award, but on a narrow ground and with reservations. As the district court correctly understood, expert witness fees cannot be awarded as a sanction under section 285. For that reason, the court invoked the court's inherent authority to justify the award of expert wit-

ness fees. *See Chambers v. NASCO, Inc.*, 501 U.S. 32, 111 S.Ct. 2123, 115 L.Ed.2d 27 (1991). While we have recognized that district courts can award expert fees in patent cases under their inherent authority, we have made clear that "not every case qualifying as exceptional under section 285 will qualify for sanctions under the court's inherent power." *Amsted Indus. Inc. v. Buckeye Steel Castings Co.*, 23 F.3d 374, 378 (Fed.Cir.1994). To the contrary, a district court may resort to its inherent power to impose sanctions only in those highly unusual cases in which the pertinent statutory remedies are plainly inadequate to address the misconduct at issue. *Amsted*, 23 F.3d at 379 ("The court should resort to its inherent power only where the rules or statutes do not reach the acts which degrade the judicial system.... [C]ourts should only resort to further sanctions when misconduct remains unremedied by those initial tools."); *see also Martin v. Brown*, 63 F.3d 1252, 1265 (3d Cir.1995) ("inherent power should be reserved for those cases in which the conduct of a party or an attorney is egregious and no other basis for sanctions exists"); *In re Rimsat, Ltd.*, 212 F.3d 1039, 1048 (7th Cir.2000). Routine use of inherent authority to impose sanctions in addition to those authorized by applicable statutes risks contravening Congress's judgment as to what sanctions are appropriate for particular misconduct. *See, e.g., Corley v. Rosewood Care Ctr., Inc.*, 142 F.3d 1041, 1059 (7th Cir.1998); *Klein v. Stahl GMBH & Co. Maschinefabrik*, 185 F.3d 98, 110 n. 10 (3d Cir.1999). Where, as here, the district court's award of attorney fees under section 285 and expert witness fees under its inherent authority are predicated on the same conduct, the district court must offer a reasoned explanation for why the award of attorney fees

and expenses under section 285 is not a sufficient sanction for the conduct in question. *See Corley,* 142 F.3d at 1058-59 ("The court also should have explained why Rule 11 was inadequate to serve the court's purposes....").

There are obviously different degrees of unjustifiable conduct, and the district court must identify the considerations that justify distinguishing "between inappropriate conduct redressable under 35 U.S.C. §§ 284, 285 and egregious conduct which justifies resort to the inherent power to sanction." *Amsted,* 23 F.3d at 378. The problem is that the standard required to justify invoking the court's inherent authority to impose sanctions is extremely vague. The standard articulated by the Supreme Court permits a court to invoke its inherent powers if the court determines "that fraud has been practiced upon it, or that the very temple of justice has been defiled." In this case, there is no suggestion that the defendants have engaged in fraudulent conduct. Instead, the court upholds the award of expert witness fees based on an abuse of judicial process, i.e., the "defiling the very temple of justice" rationale. Unfortunately, while that metaphor is colorful, it does not make for a very useful legal standard. What I take from the Supreme Court's opinion in *Chambers* and our decision in *Amsted* is that cases in which it will be considered appropriate to impose "inherent authority" sanctions in addition to those already imposed pursuant to statute or rule will be very rare. Indeed, in *Amsted* we found that the district court's exercise of its inherent power was unjustified even though the accused infringer continued to press its defenses knowing that they were meritless, burdened the court with unnecessary mo-

tions, and violated a court order. *Amsted*, 23 F.3d at 378-79. While we acknowledged in *Amsted* that the sanctioned party had engaged in inappropriate conduct, we held that it did not constitute "egregious conduct" and "bad faith" of the sort necessary to justify resort to the inherent power to sanction. *Id.* at 379.

In this case, the district court found "overwhelming" evidence of "bad faith" by Alphapharm and found that Mylan engaged in "a host of bad faith litigation tactics, which increased the burden of this litigation enormously." The court further ruled that an award of the costs associated with Takeda's employment of experts "is particularly warranted in this case" because the defendants knew that their attacks on Takeda's patent "were groundless and would only succeed if Takeda did not expend the effort and resources necessary to shine a light on the flaws in the defendants' arguments."

In my view, it is questionable whether that explanation, even as supplemented by the court's detailed analysis in its sanctions opinion of September 20, 2006, is sufficient to meet the requirement of a satisfactory explanation for invoking the inherent authority to award expert witness fees. However, it is not necessary to decide that issue in this case, because the district court made clear that the amount of its overall award did not depend on the award of expert witness fees. In its March 21, 2007, opinion, the court remarked that Takeda "would certainly be fairly entitled to an enhancement of about $3 million, with $2 million charged to Mylan and $1 million charged to Alphapharm" in light of Takeda's success and to "re-

flect the extensiveness of the misconduct here," which prolonged and increased the burden of the litigation on Takeda. Although the court did not grant the enhancement, it stated that "an enhancement to the lodestar amount will not be separately awarded" because "Takeda's expert fees are also being awarded." The court thus made clear that if it were not able to award expert witness fees, it would grant the requested enhancement of the attorney fees. For that reason, it is clear that the award of expert witness fees, even if improper, did not result in a greater total fee award than the court otherwise would have imposed if it had been limited to basing its assessment on section 285 alone.[1] I therefore concur in this court's action upholding the district court's award to Takeda. That said, however, I believe it is important to emphasize that this case should not be viewed as an invitation for district courts to impose "inherent authority" sanctions liberally in patent cases, and that such awards, even if appropriate in some cases, should be very much the exception and not the rule.

C.A.Fed. (N.Y.),2008.
Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.
549 F.3d 1381, 89 U.S.P.Q.2d 1218

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[1] Several of the expenses included in the section 285 award would appear questionable as reasonable expenditures necessary to the prosecution of the case. Those include, for example, "[b]everages while waiting at airport," client dinners, and late fees for borrowed books. The appellants have not focused on those items in their briefs, however, and therefore I would not require a remand for a specific justification of those expenses.

TAKEDA CHEMICAL INDUSTRIES, LTD., and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., Plaintiffs-Appellees, v. RANBAXY LABORATORTIES, LTD., and RANBAXY PHARMACEUTICALS, INC., Defendants, and MYLAN LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., and UDL LABORATORIES, INC., Defendants-Appellants, and WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., WATSON PHARMA, INC., and DANBURY PHARMACAL, INC., Defendants, and ALPHAPHARM PTY., LTD., and GENPHARM, INC., Defendants.

06-1364

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2007 U.S. App. LEXIS 15883

June 28, 2007, Decided

ON APPEAL from the UNITED STATES DISTRICT COURT SOUTHERN DISTRICT OF NEW YORK in CASE NO(S). 03-CV-8250, 03-CV-8253, 03-CV-8254, 04-CV-1966.

Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 2007 U.S. App. LEXIS 15349 (Fed. Cir., 2007)

JUDGES: LOURIE, BRYSON, and DYK, Circuit Judges.

OPINION

This CAUSE having been heard and considered, it is ORDERED and ADJUDGED:

Per Curiam

AFFIRMED. See Fed. Cir. R. 36.

United States District Court,
S.D. New York.

TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,

v.

MYLAN LABORATORIES, INC., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc., Defendants.

Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,

v.

Alphapharm Pty. Ltd. and Genpharm, Inc., Defendants.

Nos. 03 CIV. 8253(DLC), 04 CIV.1966(DLC).

March 21, 2007.

Anthony J. Viola, Andre K. Cizmarik, Edwards Angell Palmer & Dodge LLP, New York, NY, David G. Conlin, Barbara L. Moore, Kathleen B. Carr, Adam P. Samansky, Edwards Angell Palmer & Dodge LLP, Boston, MA, for Plaintiffs.

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Edgar H. Haug, Kevin Murphy, Jeffrey A. Hovden, Frommer Lawrence & Haug LLP, New York, NY, for Defendants Alphapharm Pty. Ltd. and Genpharm, Inc.

OPINION & ORDER

DENISE COTE, District Judge.

This Opinion addresses the size of the fee award which will be made in favor of plaintiff and patentee Takeda Pharmaceutical Company, Ltd. and its affiliate Takeda Pharmaceuticals North America, Inc. (collectively, "Takeda") against two generic drug companies: Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively, "Mylan"); and Alphapharm Pty. Ltd. and Genpharm, Inc. (collectively, "Alphapharm"). Due to the defendants' exceptional misconduct and bad faith, Takeda is awarded $11,400,000 from Mylan and $5,400,000 from Alphapharm with interest accruing from September 20, 2006 at a rate of 5.02%.

BACKGROUND

On March 10, 2006, judgment following a non-jury trial was entered in favor of Takeda and against Mylan and Alphapharm. The two generic drug companies had challenged Takeda's U.S. Patent No. 4,687,777 ("'777 Patent"), which protects the invention of the chemical compound known as pioglitazone, which is used in the treatment of diabetes. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F.Supp.2d 341 (S.D.N.Y.2006) ("Trial Opinion"). As reflected in the Trial Opinion and in the decision awarding attorney fees to Takeda for exceptional misconduct by Alphapharm and Mylan, *see Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 459 F.Supp.2d 227 (S.D.N.Y.2006) ("Sanctions Opinion"), Alphapharm and Mylan each filed baseless Paragraph IV certifications under the Hatch-Waxman Act and engaged in litigation misconduct. *Id.* at 231.Alphapharm's certification, which asserted inva-

lidity due to obviousness, "was deeply flawed and Alphapharm revised its theory again and again in a futile effort to state a prima facie case of obviousness."*Id.* Mylan abandoned its Paragraph IV theory of invalidity and at the close of discovery substituted an inequitable conduct claim. *Id.* at 249.This claim was "fatally flawed for many separate reasons."*Id.* at 248.Familiarity with the Trial and Sanctions Opinions is assumed.

After the issuance of the Sanctions Opinion, the parties litigated the amount of the award. On November 20, 2006, Takeda moved for an award of fees of $14,052,873,[1] with $9,633,149 due from Mylan and $4,419,724 due from Alphapharm.[2] It sought an enhancement of this award to reflect the particularly egregious misconduct in this case and due to the fact that the New York City market rates of intellectual property litigators are 37 to 44% higher than those charged by plaintiff's counsel. Takeda calculated that it was owed $1,661,938.70 in disbursements (of which $1,107,959 .13 is allocated to Mylan and $553,979.57 to Alphapharm), and an additional award of $1,003,443.25 to cover its expert disbursements, which it contends should be awarded through this Court's inherent power as an additional appropriate

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[1] Takeda argues that the minimal award should be approximately $12.3 million. To arrive at this figure, it applied its hourly rates as of January 2005, the *midpoint* in the litigation, to the total hours subject to the award. The requested figure of over $14 million is derived from the application of the 2006 hourly rates of the plaintiff's law firm to all of the work on which this request is made.

[2] Takeda also presents another set of figures. It asserts that, based on its current rates, it is entitled to $9,429,025 from Mylan and $4,356,011 from Alphapharm.

sanction given the nature of the misconduct in this litigation. Takeda seeks interest from September 20, 2006, the date of the Sanctions Opinion, at a rate of 5.02%, which it derives from 28 U.S.C. § 1961.

Takeda has identified tasks that it completed which related solely to Mylan or Alphapharm and those which related to both defendants. Takeda proposes that two-thirds of the joint time be allocated to Mylan and one-third to Alphapharm. It proposes this division because Mylan acted as lead defense counsel with respect to discovery of the obviousness claims,[3] and then added considerably to the complexity of the case with its untimely assertion of an inequitable conduct claim. This allocation is consistent with the complexity of the issues litigated at the trial, where the Court allocated the trial time between the defendants in the same way.

Mylan contends that Takeda is entitled to no more than $2 million in fees and expenses from Mylan, given the many problems that it asserts infect Takeda's billing records. Alternatively, it calculates the joint fees as approximately $7.3 million, which should be reduced to approximately $4.2 million and divided evenly between Mylan and Alphapharm. As for the fees attributable to Mylan alone, Mylan calculates those to be nearly $4.7 million, which should be reduced by 25% to yield approximately $3.5 million and further reduced by $1 million to reflect errors. It calculates that together these joint and Mylan-specific fees amount to an award against Mylan of just over

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[3] Mylan will enjoy a six-month exclusivity period if the '777 Patent is invalidated. Trial Opinion, 417 F.Supp.2d at 365.

$4.6 million.[4]

Alphapharm asserts that it owes Takeda between $1.38 and $1.57 million in fees. To arrive at this figure, it subtracts hours to which it objects for one reason or another, subtracts another 30% for what it asserts is excessive billing, and then applies either the hourly rate from a survey of 2004 billing rates or the 2005 rates for plaintiff's law firm.

Following its consideration of the arguments made by Mylan and Alphapharm, Takeda revised its request modestly (and not always downwardly). It now seeks attorney fees of $9,640,636 against Mylan and $4,470,397 against Alphapharm, each to be enhanced by 37 to 44%; disbursements of $1,080,504 against Mylan and $553,980 against Alphapharm; expert fees of $668,962 against Mylan and $334,481 against Alphapharm; and interest at a rate of 5.02 from September 20, 2006, the date of the decision awarding fees.

DISCUSSION

The award of attorney fees in patent infringement litigation is authorized by 35 U.S.C. § 285 ("Section 285"), which provides that "[t]he court in exceptional cases may award reasonable attorney fees to the prevailing party."In determining "reasonable" attorney fees, a court may use what is known as a hybrid lodestar approach. This approach begins with the calculation of the "lodestar" amount, an initial estimate of reasonable attorney fees calculated by multiplying

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[4] Mylan does not adequately explain how it arrived at this figure or even an approximation of this figure.

the number of hours reasonably expended on the litigation times a reasonable hourly rate for attorneys and paralegals. *City of Burlington v. Dague,* 505 U.S. 557, 559 (1992); *Blanchard v. Bergeron,* 489 U.S. 87, 94 (1989). While there is a "strong presumption" that the lodestar is reasonable, *City of Burlington,* 505 U.S. at 562 (citation omitted), district courts may "adjust [the] lodestar calculation by other factors." *Blanchard,* 489 U.S. at 94. "[T]he most critical factor" in determining the reasonableness of a fee award "is the degree of success obtained." *Farrar v. Hobby,* 506 U.S. 103, 114 (1992) (citation omitted). Consideration may also be given to the experience, reputation and ability of the attorneys as well as to the difficulty of the issues presented and the amount at stake in the litigation. *Hensley v. Eckerhart,* 461 U.S. 424, 429-30 n. 3 (1983) (citing the twelve factors listed in *Johnson v. Georgia Highway Express, Inc.,* 488 F.2d 714, 717-19 (5th Cir.1974)). A request for attorney fees "should not result in a second litigation," although the district court should provide a "concise but clear explanation of its reasons for the fee award." *Hensley,* 461 U.S. at 437.

To aid a court's calculation of the lodestar, the prevailing party must provide contemporaneous time records, affidavits, and other materials to support its application for the amount of reasonable hours expended. *McDonald v. Pension Plan of the NYSA-ILA Pension Trust Fund,* 450 F.3d 91, 96 (2d Cir.2006); *see also PPG Indus., Inc. v. Celanese Polymer Specialties Co.,* 840 F.2d 1565, 1570 (Fed.Cir.1988) ("insufficient documentation may warrant a reduction in the fees"). A reasonable hourly rate for attorney fees is a rate that is "in line with those [rates] prevailing in

the community for similar services by lawyers of reasonably comparable skill, experience and reputation." *Blum v. Stenson,* 465 U.S. 886, 896 & n. 11 (1984). The community that a district court should consider to determine the lodestar figure "is normally the district in which the court sits." *Reiter v. MTA New York City Transit Auth.,* 457 F.3d 224, 232 (2d Cir.2006) (citation omitted); *see also New York State Assoc. for Retarded Children, Inc. v. Carey,* 711 F.2d 1136, 1140 (2d Cir.1983). In determining a reasonable rate, a court may refer to American Intellectual Property Law Association ("AIPLA") surveys. *See Mathis v. Spears,* 857 F.2d 749, 755 (Fed.Cir.1988).

Alphapharm contends that Federal Circuit law-not Second Circuit law-applies to the determination of reasonable attorney fees under Section 285 and cites for support *Special Devices, Inc. v. OEA, Inc.,* 269 F.3d 1340, 1343 (Fed.Cir.2001) ("[T]he awarding of attorney fees pursuant to 35 U.S.C. § 285 is an issue unique to patent law therefore [is] subject to Federal Circuit law.").[5]*See also Serio-US Indus., Inc. v. Plastic Recovery Techs. Corp.,* 459 F.3d 1311, 1321 (Fed.Cir.2006) ("This court applies Federal Circuit law to the issue of attorney fees in patent infringement cases."). Neither *Special Devices* nor *Serio-US Indus.* considered the method for calculating the amount of an attorney fee award.[6] In any event, Al-

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[5] Takeda aptly points out that Alphapharm's counsel has taken a contrary position on its website, which opines that "[t]he law of the regional circuit is applied to determine a reasonable attorney's fee award."

[6] *Special Devices* considered the issue of whether an unquantified award of attorney fees is immediately appealable. *Special Devices,* 269 F.3d at 1343. *Serio-US Indus.* concerned whether the district court adequately supported its determination that

phapharm has not pointed to any inconsistency between Federal and Second Circuit law in the standards that are applied to calculate attorney fees. The Federal and Second Circuits both emphasize that the calculation of a reasonable attorney fee may begin with the lodestar figure and relies upon the district court's exercise of discretion to increase or decrease that figure in light of other factors. *See View Eng'g, Inc. v. Robotic Vision Sys., Inc.*, 208 F.3d 981, 988 (Fed.Cir.2000) (upholding district court's reduction of lodestar after consideration of relevant factors to reach final sanction award); *Orchano v. Advanced Recovery, Inc.*, 107 F.3d 94, 98 (2d Cir.1997) (citing *Hensley*, 461 U.S. at 434) (district court may adjust lodestar upward or downward after due consideration of other factors, including the "degree of success obtained").

The Federal Circuit has emphasized that a reasonable attorney fee is "a determination that lies primarily within the discretion of the district court," which may "consider all the relevant circumstances in a particular case." *Junker v. Eddings*, 396 F.3d 1359, 1365-66 (Fed.Cir.2005).

> [T]rial judges enjoy discretion to award attorney fees for good reason. After presiding over the preparation and trial of the case, the trial judge can best weigh the relevant considerations, such as the closeness of the case, the tactics of counsel, the flagrant or good faith character of the parties' conduct, and any other factors contributing to imposition of punitive

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the case was "exceptional" and merited an award of attorney fees. *Serio-US Indus.*, 459 F.3d at 1322.

> sanctions or to fair allocation of the burdens of the litigation.

Perricone, M.D. v. Medicis Pharm. Corp., 432 F.3d 1368, 1380-81 (Fed.Cir.2005) (citation omitted); *see also Hensley*, 461 U.S. at 437 (district court's exercise of discretion to determine fee award is warranted by its superior understanding of the litigation and the "desirability of avoiding frequent appellate review of what essentially are factual matters."). Thus, the

> district court's inherent equitable power and informed discretion remain available in determining the level of exceptionality rising out of the offender's particular conduct, and in then determining, in light of that conduct, the compensatory quantum of the award, including the amount of attorney fees, what if any expenses shall be included, and the rate of prejudgment interest, if any, on the award.

Mathis, 857 F.2d at 754.

A. Takeda is Entitled to a Substantial Fee Award.

Takeda seeks to recover at a minimum approximately $14 million in attorney fees through this application. This sum is entirely reasonable and amply supported by the records it has submitted with its request. This Court has supervised this litigation from its inception and is intimately familiar with the work done by all counsel, the challenges presented in defending against the defendants' shifting attacks on the '777 Patent, the intensity with which these two lawsuits were fought, and the complexity of the evidentiary and scientific problems posed by the litigation.

A lodestar calculation by Takeda in the vicinity of approximately $20 million would not have been surprising. The defense of an extraordinarily profitable pharmaceutical was at stake here, a drug that had contributed to a revolution in the treatment of a serious and widespread disease. The work done by Takeda's counsel was uniformly excellent. Its written submissions were reliable; it made factual statements that were rooted in the record; and it presented legal arguments that reflected a thorough understanding of the relevant law and were well researched. In the many pretrial conferences held during the course of discovery and in preparation for the trial, its counsel was always well-prepared, courteous and knowledgeable. Managing discovery in this litigation, which included an enormous production of decades-old Japanese documents, was extraordinarily demanding. Takeda's lawyers responded effectively and swiftly to a stream of attacks on the patent, attacks which kept shifting right up to the time of trial summations. These attacks drew from different scientific disciplines; some were based on the molecular structure of the compounds Takeda investigated; others focused more on the scientific method Takeda employed in its selection of pioglitazone for development.

The quality of Takeda's trial presentation is particularly notable. Complex scientific materials were presented in an entirely accessible manner. Volumes of documents were organized and synthesized. The briefs, affidavits constituting witnesses' direct testimony, and proposed findings included citations that provided quick access to the trial record. None of this could have happened without a dedicated effort by a

well-coordinated team. In sum, Takeda was well represented in this litigation and this Court was greatly assisted by the fine work done by Takeda's counsel.

Mylan and Alphapharm contend that the fee request is unreasonable. They assert that attorney fees have been awarded in only two Abbreviated New Drug Application ("ANDA") cases, and that in neither did the award exceed $2 million. *See Yamanouchi Pharm. Co ., Ltd. v. Danbury Pharmacal, Inc.*, 51 F.Supp.2d 302, 309 (S.D.N.Y.1999) (granting $1,635,440 in attorney fees); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 264 F.Supp.2d 753, 784 (S . D.N.Y.2003) (granting $1,523,580.85 in attorney fees). Reviewing all awards in patent cases under Section 285 since 2000, Mylan asserts that no fee award has exceeded $5.2 million. Alphapharm located two awards far surpassing that amount. The court in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833(RPP), 2002 WL 1733681, at *16 (S.D.N.Y. July 26, 2002), after intensive litigation over the validity of a pharmaceutical patent, awarded almost $27 million in attorney fees and disbursements under Section 285 and, over defendants' objection, also awarded sanctions of almost $6 million for expert fees and prejudgment interest.[7] Over a decade ago in *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, No. H-89-3203, 1993 WL 268680, at 5-6 (S.D.Tex. Feb. 17, 1993), the court awarded attorney fees of almost $18 million and costs of over $235,000 pursuant to Section 285 following a jury trial.

It is unnecessary to examine the awards made in

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[7] The defendants also objected to the payment of computer research fees. *Bristol-Myers*, 2002 WL 1733681, at *14.

other cases. This Court is well familiar with the record in this case, the quality of work performed here, the degree of success achieved by Takeda, and the general cost of complex litigation in New York City. An award of attorney fees of approximately $14 million is entirely justified, and for the reasons described below, even a significantly larger award than the lodestar amount would be justified.

B. Size of Staff

None of the specific attacks which the defendants have made on the size of the fee request here has merit. Mylan contends that Takeda's counsel overstaffed the case and spent too much money to defend a single patent.[8] Mylan asserts that this reflects a lack of judgment. In a similar vein, Alphapharm complains that Takeda is seeking reimbursement for the work of 72 separate persons.

While it is true that over the course of this roughly three-year litigation Takeda's counsel used many professionals, an examination of the distribution of the work reflects a well-organized team effort.[9] Two partners devoted approximately three thousand hours

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[8] Alphapharm makes precisely the opposite point. It contends that the amount of the fee request is excessive because Takeda's sales exceed $2 billion a year, in effect arguing that Takeda can afford the expense of litigation.

[9] The discussion in the text ignores the hours billed by a professional when those hours amounted to less than 200 hours over the course of the case. Two partners and one counsel worked less than 100 hours; many associates worked less than 200 hours. This pattern is consistent with what would be expected in major litigation: personnel are pulled in to help with a discrete task or when the demands of meeting a particular deadline require it.

each to this effort, with two other partners working just over 1,000 hours on the matter.[10] Two counsel worked on the matter: one for just over 1,000 hours and one for less than 500 hours. Three associates each worked over 3,000 hours; three others worked less than 2,000 hours apiece; and eight others worked less than 1,000 hours apiece. Only one contract attorney worked more than two thousand hours, while two others each worked over 1,000 hours, and fourteen worked more than 200 hours. Thus, the bulk of the work was appropriately concentrated in the hands of a team of professionals with different levels of experience and expertise. An examination of the billing records does not reflect overstaffing.

Mylan asserts that too many professionals attended the same meetings or court appearances, and that Takeda should not be reimbursed for the duplicative use of personnel. Alphapharm makes the same point, citing attendance at three meetings in particular. This argument is without merit. It would be impossible to run litigation of this magnitude without multiple attorneys attending some of the same meetings and court appearances. The defendants have not succeeded in pointing to any abuse in this regard by Takeda's counsel.

To the extent that Mylan questions the number of Takeda professionals who attended the trial, that objection can also be swiftly rejected. Takeda had no more professionals attending the trial than did the defendants. In addition, because the Court took direct testimony by affidavit and was thoroughly familiar

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[10] One of the partners acted as the senior partner on the matter; two others divided the bulk of the trial work between them.

with that testimony, the trial exhibits, and the parties' arguments before the trial began, and because the trial days were devoted exclusively to the cross-examination and re-direct examination of witnesses and summations, the trial was conducted in a relatively brief time-frame when measured against the complexity of the evidentiary and legal issues. The careful preparation and efficient presentation by trial counsel permitted the trial to move ahead apace, without unnecessary delay. There was no overstaffing at trial.

C. Survey Comparisons

Relying on an AIPLA survey (the "Survey"), Alphapharm contends that Takeda's request is too high since the average total cost for patent infringement litigation in New York City is just over $6 million. The Survey, which was conducted in 2005, received thirty-five responses from attorneys practicing in the New York City CMSA.[11] They reported that in the typical patent infringement litigation with no unusual complications in which over $25 million was at stake, the average cost of the litigation in 2004 was just over $6 million, with one-quarter of the cases exceeding $8 million.

Takeda attacks the reliability of the Survey, noting among other things that too few respondents provided information to make its results reliable.[12] *See*

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[11] It is not clear how much of the area that surrounds New York City was included in what the Survey labels as the New York City CMSA.

[12] The Survey does not indicate its return rate, but does note that usable questionnaires were received from 1,558 individuals.

Yurman Designs, Inc. v. PAJ, Inc., 125 F.Supp.2d 54, 57 (S.D.N.Y.2000) (rejecting AIPLA survey of hourly rates for a New York City intellectual property attorney because fewer than ten percent of attorneys surveyed responded to the inquiry). It is unnecessary to resolve the parties' dispute as to the reliability of the Survey since the Survey's results actually confirm the reasonableness of the Takeda fee request.

Although only one patent was at stake here, the profitability of the patent for Takeda, and the incentive that those profit figures provided to the defendants, meant that the litigation over the validity of the '777 Patent was enormously important to all parties. Moreover, because Mylan altered course in midstream, abandoning its theory of obviousness and opting instead to pursue a theory of inequitable conduct, the litigation was equivalent to two atypical and massive patent cases.[13] Compared to "average" litigation with something over $25 million at stake, this case was unusual litigation, with billions of dollars at stake. Incurring costs that triple or quadruple the cost of the "average" case reflected in the Survey would be entirely unsurprising.

D. Mylan's Experts

Mylan has reserved the bulk of its attack on the fee

Only 299 of that number answered the question at issue here, and *only 35* of the 299 came from the "NYC CMSA".

[13] Mylan itself has estimated that an ANDA filer would anticipate spending between $5 and $12 million to litigate a single ANDA case. It is interesting that neither Mylan nor Alphapharm has offered evidence of their own attorney fees in this litigation as a point of comparison with Takeda's fee request.

request for the opinions offered by two purported experts. Takeda has moved to strike the declarations from James H. Wallace, Jr. ("Wallace") and John J. Marquess ("Marquess").

Marquess, the President of Legal Cost Control, Inc., identifies himself as a fee auditor. With just nine days of work, he contends that he conducted a meaningful audit of millions of dollars in billings by Takeda's counsel. Notably, Mylan did not request Marquess to provide any opinions regarding "the substantive nature or quality" of the professional services. Instead, Marquess represents that he reviewed "each" billing line item and considered it in light of "reasonable billing practices within the legal and professional community," or what he terms "generally accepted legal and professional billing practices."

A few examples from his report suggest the quality of his work. His procedures include "unblocking" entries in which a single time charge lists multiple activities. To unblock the entry, he divides the time through a pro-rata allocation to each activity without making any distinction based on the complexity of the activity or how the time was or would likely have been spent on a single task. As another example, he questions the general practice among law firms of using contract attorneys and contends that a law firm may not properly charge its client a "mark up" on the cost of employing such attorneys.

Mylan has not shown that Marquess' opinion qualifies as admissible expert evidence. Marquess has no experience in patent law or complex litigation. He has no familiarity with the substance of the Takeda liti-

gation, and made no effort to become familiar with it. His work purports to apply generally accepted billing practices, but Mylan has failed to show that there is any such standard, or that Marquess has followed *any* recognized standard in preparing his evaluation of the Takeda fee request. Thus, the Marquess report is rejected to the extent it is offered as an expert opinion. *See In re Worldwide Direct, Inc.*, 316 B.R. 637, 642-43 (D.Del.2004) (rejecting Marquess, whose opinion was offered under the name of his firm, as an expert fee auditor).[14]

Even if the Marquess opinion were admissible as an expert opinion, it is singularly unhelpful. Because of his lack of experience in complex litigation much less patent litigation, his opinion about the reasonableness of the fee request here is entitled to essentially no weight. Moreover, his method of reviewing the time charges is deeply flawed. For instance, he has identified no reasonable standard that would suggest it is appropriate to apportion time equally among several tasks performed during a block of time without consideration of the nature of the tasks. He criticizes the use of contract attorneys without any analysis of the types of tasks they performed in this case and whether their use in fact resulted in efficiencies for Takeda. In complex litigation, contract attorneys are routinely used by well-established law firms who supervise their work. Mylan has failed to show that it

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[14] Remarkably, Marquess did not report that the court in *Worldwide* had rejected him as an expert. Although he and Mylan try to excuse the omission, their failure to disclose the *Worldwide* court's rejection of his opinion as admissible expert evidence was a breach of their duties to the court.

was inappropriate for Takeda's counsel either to use contract professionals in this case or to use them to the extent that it did.[15]

Mylan asks that Marquess' opinion at least be accepted as summary evidence. To the extent that summary figures from the Marquess report are also contained in Mylan's brief, they have been considered in connection with Mylan's arguments on this application.

Wallace, the second proffered expert, is a partner at Wiley Rein & Fielding LLP.[16] He represents that he has "handled" patent litigation, including ANDA trials for Mylan during the last eleven years. After reviewing the Sanctions Opinion and Takeda's briefs and affidavits in support of its November 2006 fee application, he opines that Takeda's request is "grossly excessive." As a point of comparison, he describes the fees his law firm incurred in two patent cases: a 2005 case in which he represented Mylan,

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[15] It is interesting to note that Mylan has not proffered that it was able to litigate this case without the use of contract professionals.

[16] Wallace has charged Mylan $595 per hour, which he describes as his "normal rate." This disclosure of Wallace's "normal" fee is additional evidence that Alphapharm's objections to the hourly rates charged by Takeda's lawyers is utterly baseless. Wallace has provided surprisingly little information about himself or his firm, but it does not appear that he is based in New York City. It appears that he bases his practice in Washington, D.C.; he is not admitted to practice in either the Southern or Eastern District of New York, and although he is admitted to practice before many Courts of Appeals, he is not admitted to practice before the Court of Appeals for the Second Circuit.

including at a nine-day trial;[17] and a 2001 through 2003 case litigating a non-pharmaceutical patent. His other point of comparison is his survey of ANDA and non-ANDA cases since 2000.

Wallace's opinion is inadmissible since he has failed to conduct an adequate investigation of this litigation so that he could render a helpful opinion. *See Brooks v. Outboard Marine Corp.*, 234 F.3d 89, 92 (2d Cir.2000). He did not examine the Trial Opinion, the time records submitted by Takeda that describe in detail the work its attorneys performed on this matter, or otherwise do the work which would have given him a reasonable basis to evaluate the fee request and compare it to the cost of any other litigation with which he is familiar.

Even if it were admissible, Wallace's opinion would be entitled to no weight given the inadequacy of his investigation of the Takeda matter. Moreover, his points of comparison show that his opinion is utterly unreliable. In the 2005 litigation which he handled for Mylan, Wallace pointed out to that court that a generic company challenging a patent in ANDA litigation would ordinarily incur "far less" in attorney fees than the patentee. Despite the existence of this obvious and relevant point of reference, Wallace pointedly does *not* offer Mylan's attorney fees in the

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[17] Mylan's attacks on the adequacy of the Takeda submission in support of the fee request stand in stark contrast to the positions it took in the 2005 case in which it was represented by Wallace. In that case, Mylan submitted billing records which indicated only the monthly charge for "professional fees" without any detail from which to determine which attorneys had worked on the matter, their hourly rate, their hours or the tasks they performed.

Takeda matter as a point of comparison. Moreover, his "survey" of Section 285 fee awards omits reference to the award of over $32.6 million in *Bristol-Myers* in 2002. Sadly, it would appear that Wallace has let his relationship with Mylan interfere with his obligation to provide an opinion based on careful and considered analysis.[18]

E. Allocation Between Mylan and Alphapharm

Mylan challenges the allocation of fees and costs proposed by Takeda. In preparation for this fee request, Takeda's counsel reviewed all of its contemporaneous time entries to allocate the time among work performed directly on issues presented by Mylan, by Alphapharm or by both defendants. As explained above, it has allocated two-thirds of the joint time to Mylan.[19]Mylan contends that it was inappropriate for Takeda's counsel to rely on an after-the-fact allocation of tasks to separate those performed because of the litigation with Mylan from those associated with the Alphapharm litigation. Takeda's procedures for

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[18] Since Mylan did not give notice of its intent to rely on expert testimony, Takeda has been deprived of an opportunity to take discovery of the experts. Since neither expert has provided opinion testimony that is helpful to the Court, it is unnecessary to delay a ruling on Takeda's application to give it an opportunity to take such discovery.

[19] As the first ANDA filer, Alphapharm was entitled to enter the market six months in advance of any generic drug competitor. *See* Trial Opinion, 417 F.Supp.2d at 365. Alphapharm lost that advantage to Mylan by January 2004, when the Food and Drug Administration found that Alphapharm was unable to make a bioequivalent to the patented drug. *Id.* & n. 27. Plaintiff's counsel originally recorded all of their time defending the '777 Patent under a single matter assigned to Mylan. In December 2005, it created separate matter numbers for Mylan and Alphapharm.

reviewing its contemporaneously entered billing records to make an appropriate allocation between Alphapharm and Mylan were perfectly reasonable and acceptable.

Mylan proposes that the "joint" time be evenly divided between the parties or disallowed, but has little or no reasoned response to Takeda's argument that it should pay for two-thirds of the joint time. Takeda's suggestion for the unequal division of the cost of the joint work is adopted. Mylan added very significantly to the expense, burden and complexity of the litigation. It is only fair to Alphapharm to require Mylan to bear more than half of the expense associated with the "joint" tasks. If the positions Mylan took during the litigation had been meritorious, this analysis might be different. As explained in the Trial and Sanctions Opinions, however, Mylan's litigation strategies were adopted in bad faith.

F. Contemporaneity and Block Billing

To support its fee request, Takeda submitted over 500 pages of spreadsheets containing over 8,000 contemporaneous time entries.[20] The entries list a timekeeper, the hours spent, and a narrative description of the task performed.

Mylan argues that some of the time entries represent improper "block" billing. Alphapharm asserts that 158 billing records reflect work of more than 15 hours in a single day. When these entries are examined with an understanding of the billing practices used by

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[20] The defendants' assertion that Takeda's counsel has not produced contemporaneous time records is flat wrong.

Takeda's law firm, there is nothing misleading or inappropriate about them. The defendants' attacks are rejected.

Finally, Alphapharm asserts that the bills are not sufficiently detailed to support a review for reasonableness. It is wrong. In the Court's experience, the records its counsel maintained reflect the standard practices of major law firms, in particular in the level of detail they record. In the current business environment for the legal profession, law firms must be prepared to respond to clients' detailed inquiries about their bills. The records that support this fee request would provide ample scope for a detailed review by the client, and more than adequate scope for review by the court that has overseen the litigation.

G. Clerical Work and Miscellaneous Matters

Alphapharm and Mylan complain that Takeda used attorneys to perform purely clerical tasks. While it is important that attorneys delegate tasks that can be performed by less highly compensated personnel, it is unrealistic to expect that all of the work that might be described as "clerical," for example preparing and organizing materials for discovery and trial, can be delegated. In a complex case, such work requires a coordinated effort by a team of professionals that includes attorneys and paralegals. For example, no competent trial lawyer will allow exhibits to be prepared and organized for witnesses and the Court without the attorneys who will be responsible for presenting the evidence in the courtroom directly supervising that effort. Alphapharm, whose own attorneys have sought reimbursement in other patent litigation

for virtually identical work, has not shown that Takeda's fee request is unreasonable in this regard.

Alphapharm also contends that work by library and administrative personnel is purely clerical and cannot be recovered. Takeda has shown that these individuals have billed time to this litigation when they were conducting research or other tasks specific to this case. The time is properly compensable.

The Court has reviewed each of the defendants' arguments about other specific items in the Takeda fee request. Each of them is rejected whether or not specifically addressed in this Opinion. In some instances, Takeda has made adjustments. In others, the defendants' complaints rely on a misrepresentation of the documentation. In others, the complaints are not well-founded for entirely separate reasons. The objections related to the amount of time spent conducting legal research on the issue of personal jurisdiction, on the preparation of and response to discovery requests, and on editing two privilege logs,[21] are specifically denied. Finally, Alphapharm and Mylan contend that the time spent preparing an animation for use at trial can only be recouped as a cost pursuant to 28 U.S.C. § 1920, and not as attorney fees. When attorneys, as opposed to outside vendors, work on such a project, their time is properly recoverable pursuant to Section 285.[22]

H. Hourly Rates

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[21] The logs were over 200 pages long and contained close to 4,000 entries.

[22] Alphapharm's own counsel has sought to recover its fees for similar work in other litigation.

As already noted, the community in which the litigation is conducted provides the baseline for determining a reasonable hourly rate for attorney fees, and a court may draw upon "its knowledge of the relevant market when determining the reasonable hourly rate." *McDonald*, 450 F.3d at 96-97. Moreover, a district court should use "current rather than historic hourly rates," *Reiter*, 457 F .3d at 232 (citation omitted), in setting the hourly rate for the lodestar calculation.

Takeda has calculated a lodestar figure using its September 2006 rates for its law firm's professionals, rather than their hourly rates at the time they performed the work. It has also calculated a lodestar based on the rates that existed as of January 2005, roughly the midpoint of the litigation, as an alternative, more conservative measure. Takeda contends, however, that the award should be enhanced in either case because its counsel's fees were lower than the prevailing rates of intellectual property litigators in New York City.

Two sets of rates illustrate Takeda's point. The 2006 rates for the partners who worked on this matter ranged from $375 to $600, with an average of $498. Those rates for associates ranged from $175 to $385, with an average of $278. The average rates for the partners who worked on Takeda's litigation were over 20% lower than the effective rates of intellectual property litigators in New York City in 2004 and 2005, as reported by the PricewaterhouseCoopers LLP 2005 and 2006 Billing Rate & Associate Salary Surveys ("PWC Surveys"). The spread was larger for

the associates working on Takeda's litigation. *See also Yurman,* 125 F.Supp.2d at 55, 58 (finding $520 hourly rate for a New York City copyright and trademark litigation partner to be reasonable in 1999).

Alphapharm contends that the 2006 rates for the partners who worked on the Takeda matter are higher that the average billing rate for intellectual property partners in New York City, as reflected in the AIPLA survey for 2004. It admits that the rates for associates who worked on the Takeda matter are lower than those in the survey, but contends that it is significant that Takeda did not submit affidavits for the associates reporting on their level of experience and skill. These and similar arguments are unconvincing. Alphapharm does not deny that the PWC Surveys are far more reliable than the AIPLA survey since they contain more detailed information that is specific to New York City and the timeframe for our litigation.

Alphapharm urges that the 2005 and not the 2006 billing rates should be used in any event since most of the litigation occurred in 2005, and the rates of plaintiff's law firm were affected by its merger in November 2005 with another law firm. The 2006 rates are more appropriate. There is no requirement that a court apply historic rates, and the 2006 rates are entirely reasonable when judged against the relevant community standard.

I. Enhancement

Mylan opposes any enhancement to Takeda's lodestar

recovery. It asserts that the lodestar figure is recognized under the law as reasonable, and that an enhancement is only warranted when there is either excessive delay in payment or public policy support for it.

Takeda would certainly be fairly entitled to an enhancement of about $3 million, with $2 million charged to Mylan and $1 million charged to Alphapharm. It would reflect Takeda's degree of success, which was complete on each and every one of the many points in contention, and the defendants' outrageous litigation conduct, which amply justifies sanctions beyond the out-of-pocket cost of this litigation to Takeda.

What is truly exceptional here is the cascade of attacks each defendant made on the '777 Patent. If the defendants had simply pursued the theories presented in their Paragraph IV certifications, the cost of litigation would have been far lower and a simple award of the lodestar calculation may have been warranted. They did not rest there, though. In each instance the Section 355 Statement was so lacking in merit that it was entirely abandoned by the time of trial. The parties increased the cost and burden of this litigation enormously through their shifting theories of attack, none of which was meritorious or adopted in good faith. None of the theories reflected a careful analysis of the relevant documents and the application of sound science to that analysis. Alphapharm's extensive list of asserted and then abandoned obviousness theories is summarized in the Sanctions Opinion. Sanctions Opinion, 459 F.Supp.2d at 240-41. Mylan resisted discovery on the theory of

obviousness contained in its Section 355 Statement, and then after the close of discovery sought to substitute another frivolous theory of obviousness. It also asserted an inequitable misconduct claim that was thoroughly discredited at trial. *Id.* at 246-50.

The award of attorney fees to Takeda without an enhancement already compensates it, of course, for the extra expense incurred in responding to this litany of meritless theories and the associated misconduct. More would be entirely appropriate, however, to reflect the extensiveness of the misconduct here, in particular its repetitive nature. A wildly successful pharmaceutical patent will of course draw attacks. There is a strong public interest, as acknowledged by the statutory scheme, in challenging patents that keep the price of patented pharmaceuticals high. There should be no incentive, however, for litigation that is prolonged and complicated by a series of attacks undertaken without a good faith basis and without a sound basis in science. Science, medical research, and the court system demand better. Because Takeda's expert fees are also being awarded, however, an enhancement to the lodestar amount will not be separately entered.

J. Expenses

Takeda has requested over $1.6 million in reimbursable expenses under 35 U.S.C. § 285. Alphapharm contends that Takeda cannot recover expenses beyond those identified in 28 U.S.C. §§ 1821 and 1920.[23]

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[23] 28 U.S.C. § 1821 provides for witness fees. It states in pertinent part

(a) (1) Except as otherwise provided by law, a witness in attendance at any court of the United States, or before a United States Magistrate Judge, or before any person authorized to take his deposition pursuant to any rule or order of a court of the United States, shall be paid the fees and allowances provided by this section ....

(b) A witness shall be paid an attendance fee of $40 per day for each day's attendance. A witness shall also be paid the attendance fee for the time necessarily occupied in going to and returning from the place of attendance at the beginning and end of such attendance or at any time during such attendance.

28 U.S.C. § 1920 enumerates costs associated with litigation.

Taxation of costs

A judge or clerk of any court of the United States may tax as costs the following:

(1) Fees of the clerk and marshal;

(2) Fees of the court reporter for all or any part of the stenographic transcript necessarily obtained for use in the case;

(3) Fees and disbursements for printing and witnesses;

(4) Fees for exemplification and copies of papers necessarily obtained for use in the case;

(5) Docket fees under section 1923 of this title;

(6) Compensation of court appointed experts, compensation of interpreters, and salaries, fees, expenses, and costs of special interpretation services under section 1828 of this title.

The bill of costs submitted here amounts to $229,568.81, all of which is for items not included in the Section 285 request.

Alphapharm's statement of the law is incorrect. The Federal Circuit has interpreted the term "attorney fees" under Section 285"to include those sums that the prevailing party incurs in the preparation for and performance of legal services related to the suit." *Mathis,* 857 F.2d at 757 (citation omitted). As an exception to the American Rule that each party bears its own attorney fees and expenses, Section 285 was expressly added by Congress to provide attorney fees and expenses in "exceptional cases." This provision is intended

> to discourage conduct which fell within the scope of "exceptional," by requiring the party acting exceptionally to bear the expenses of the opposing party. It would be inconsistent with the intent of § 285 to limit the prevailing party to something less.

Central Soya Co., Inc. v. Geo. A. Hormel & Co., 723 F.2d 1573, 1578 (Fed.Cir.1983) (citation omitted). With this understanding, the Federal Circuit has upheld district courts' discretionary grant of expenses to prevailing parties under Section 285 beyond expenses enumerated in Sections 1821 and 1920. *Id.* (upholding district court's discretionary grant of expenses under Section 285); *Mathis,* 857 F.2d at 758 (finding that "it would be inconsistent with the intent of Section 285 to limit prevailing-party Hydro to something

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A bill of costs shall be filed in the case and, upon allowance, included in the judgment or decree.

less than the fees and expenses to which it was subjected by Mathis in this 'very exceptional' case of 'gross injustice' " and that "28 U.S.C. §§ 1920 and 1821 are not here applicable.").

Mylan asserts that the expenses should be allocated equally and the amount reduced dramatically. Both defendants contend that the award of expenses should be denied because Takeda did not provide invoices to document its disbursements. Takeda supported its request for reimbursement of disbursements with a computer printout of the contemporaneous billing entries for the disbursements. This documentation is sufficient.

As far as the individual items which Mylan contends are not reimbursable expenses, its contention is rejected. It has not identified one item that is not a customary and appropriate expense associated with litigating a complex patent case, or indeed, any complex litigation. As Takeda points out, Mylan's counsel has sought reimbursement for these very kinds of expenses in other patent litigation.

K. Expert Fees

Takeda admits that its expert witness fees cannot be awarded under Section 285 as ordinary litigation expenses. *See Amsted Indus. Inc. v. Buckeye Steel Castings Co.*, 23 F.3d 374, 377 (Fed.Cir.1994). It seeks reimbursement of these fees under this Court's inherent power to impose sanctions for bad faith and vexatious conduct. *Chambers v. Nasco, Inc.*, 501 U.S. 32, 46 (1991)."[I]f in the informed discretion of the court," neither the applicable statute nor the Federal Rules

of Civil Procedure sanctioning bad-faith litigation conduct "are up to the task, the court may safely rely on its inherent power." *Id.* at 50.Specifically, a district court, "in the exercise of its discretion and inherent equity power," may "include an award of reasonable expert witness fees in excess of the $30/day attendance fee specified in 28 U.S.C. § 1821." *Mathis*, 857 F.2d at 759. *See also Amsted,* 23 F.3d at 378; *Bristol-Myers Squibb*, 2002 WL 1733681, at *14.

Takeda's request is granted. For the reasons already described in detail in a prior Opinion, "[t]he evidence of Alphapharm's bad faith is overwhelming."Sanctions Opinion, 459 F.Supp.2d at 243. Similarly, Mylan engaged in a host of bad faith litigation tactics, which increased the burden of this litigation enormously. These included the presentation of factually indefensible positions from its ANDA filing straight through to its submissions in opposition to the motion for sanctions. *Id.* at 247-48.

An award of the costs associated with Takeda's employment of experts is particularly warranted in this case. To analyze fairly and correctly the challenges that the defendants made to the '777 Patent, it was necessary for the Court to understand the principles and issues associated with several scientific disciplines. Takeda brought to this task experts of impeccable credentials who spent the time that they needed to master the facts relevant to the challenges to the patent so that they could present the relevant scientific principles and their expert opinions in an accessible and helpful manner. Their testimony was critical to the findings of fact entered in the Trial Opinion.

Takeda's approach to the use of experts stood in stark contrast to that of the defendants. As a general matter, the defendants' experts were far less impressive, had not done their homework regarding the issues at stake in this case, and often ventured from their fields of expertise. The defendants' performance in this regard provides further evidence that they well understood that their attacks on the '777 Patent were groundless and would only succeed if Takeda did not expend the effort and resources necessary to shine a light on the flaws in the defendants' arguments and if the Court did not spend the time necessary to learn the relevant science and understand the evidentiary record created by the trial submissions.

L. Interest

Takeda seeks an award of interest on the attorney fee award from the date the Sanctions Opinion was issued: September 20, 2006. It contends that such an award is appropriate under Section 285, or alternatively as an exercise of the Court's inherent equitable power as a sanction for bad faith conduct.

According to 28 U.S.C. § 1961, "[i]nterest shall be allowed on any money judgment in a civil case recovered in a district court.... Such interest shall be calculated from the date of the entry of the judgment, at a rate equal to the weekly average 1-year constant maturity Treasury yield."Post-judgment interest is correctly calculated "from the date of the judgment establishing the right to the award." *Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 804 (Fed.Cir.1990).*See also Mathis*, 857 F.2d at 760 (in-

terpreting 28 U.S.C. § 1961 to find that "[i]nterest on an attorney fee award ... runs from the date of the judgment establishing the right to the award, not the date of the judgment establishing its quantum.").

Takeda is awarded interest accruing from the date of the Sanctions Opinion, September 20, 2006. Alphapharm's characterization of Takeda's request as a request for prejudgment interest is simply incorrect. Moreover, its reliance on *Beatrice Foods Co. v. New England Printing & Lithographing Co.*, 923 F.2d 1576 (Fed.Cir.1991), is unpersuasive. *Beatrice* vacated an award of enhanced damages under 35 U.S.C. § 284 and noted that prejudgment interest under that section could be granted in any event only for the primary damage award and not for enhanced damages under Section 284. *Id.* at 1580. *Beatrice* did not address post-judgment interest for an award under Section 285. As such, it fails to support Alphapharm's argument that Takeda should not be awarded interest on the fee award granted today from the date of the Sanctions Opinion either under Section 285 or through this Court's inherent power.

CONCLUSION

Takeda is awarded attorney fees, expenses, and expert fees in the amount of $11,400,000 from Mylan and $5,400.000 from Alphapharm, with interest accruing from September 20, 2006 at a rate of 5.02%.

SO ORDERED.

S.D.N.Y.,2007.
Takeda Chemical Industries, Ltd. v. Mylan Laborato-

ries, Inc.
Not Reported in F.Supp.2d, 2007 WL 840368 (S.D.N.Y.)

United States District Court,
S.D. New York.

TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,
v.
MYLAN LABORATORIES, INC., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc., Defendants.

Takeda Chemical Industries, LTD. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,
v.
Alphapharm PTY. LTD. and Genpharm, Inc., Defendants.

Nos. 03 CIV. 8253(DLC), 04 CIV.1966.

Sept. 20, 2006.

Background: Patentee brought action against generic drug companies alleging infringement of patent directed toward chemical compound known as pioglitazone when defendants filed Abbreviated New Drug Application (ANDA) to make generic form of pioglitazone. Court granted judgment in favor of patentee, 2006 WL 618424.Patentee brought motion for attorney fees on basis that case was exceptional.

Holdings: The District Court, Cote, J., held that:
(1) competitor forfeited any right to rely on opinion of counsel in opposing patentee's motion for award of attorney fees;
(2) competitor breached duty of due care that was imposed by Hatch-Waxman Act on persons who filed ANDA certifications;
(3) competitor engaged in litigation misconduct following filing of its ANDA certification;
(4) competitor's pursuit of claim that patentee had

engaged in inequitable conduct was frivolous;
(5) other competitor's filing of ANDA application and its statement of reasons that it believed that patent was invalid were in bad faith;
(6) patentee was entitled to award of attorney fees on basis that case was exceptional for other competitor's pursuit of inequitable misconduct claim after close of fact discovery;
(7) other competitor's additional misconduct warranted award of attorney fees; and
(8) Hatch-Waxman Act did not immunize baseless ANDA filings or pursuit of frivolous ANDA litigation in bad faith.

Motion granted.

Anthony J. Viola, Andre K. Cizmarik, Edwards Angell Palmer & Dodge LLP, New York, NY, and David G. Conlin, Barbara L. Moore, Kathleen B. Carr, Edwards Angell Palmer & Dodge LLP, Boston, MA, for Plaintiffs.

Edgar H. Haug, Kevin F. Murphy, Jeffrey A. Hovden, Frommer Lawrence & Haug LLP, New York, NY, for Defendants Alphapharm Pty. Ltd. and Genpharm, Inc.

Martin B. Pavane, Edward V. Di Lello, Mindy H. Chettih, James P. Doyle, Cohen, Pontani, Lieberman & Pavane, New York, NY, for Defendants Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc.

OPINION & ORDER

COTE, District Judge.

On March 10, 2006, judgment was entered following a non-jury trial in favor of plaintiff and patentee Takeda Pharmaceutical Company, Ltd. (formerly Takeda Chemical Industries, Ltd.), and its affiliate Takeda Pharmaceuticals North America, Inc. (collectively, "Takeda") and against two generic drug companies, Alphapharm Pty. Ltd. and Genpharm, Inc. (collectively, "Alphapharm") and Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively, "Mylan"), in connection with the latters' challenges brought under the Hatch-Waxman Act to Takeda's U.S. Patent No. 4,687,777 ("'777 Patent"), which protects the invention of the chemical compound known as pioglitazone. *Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.*, 417 F.Supp.2d 341 (S.D.N.Y.2006) ("Opinion"). Pioglitazone is a highly successful drug used in the treatment of diabetes.

Takeda has now moved for an award of attorneys' fees against both defendants, arguing that this is an exceptional case. Takeda contends that each of the defendants lacked a good faith basis for its Hatch-Waxman Act Paragraph IV certification and engaged in litigation misconduct. Takeda's motion is granted.[1]

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[1] The Opinion mistakenly described Howard Rosenberg as one of Alphapharm's trial experts. Opinion at 381 n. 64. Howard Rosenberg was a fact witness for Alphapharm. Mylan served Michael Rosenberg's expert report, but before trial withdrew its proffer of him as an expert. The Opinion also erred when, in a moment of unintentional literary homage, it identified Alphapharm's expert Brian Wright, a Professor of Economics at the University of California at Berkeley, as Richard Wright. *Id.* at 345.

An award of attorneys' fees should not be made without a careful consideration of the litigation as a whole and the parties' arguments. The framework established by Congress for accelerating the approval process for generic versions of established drugs, however, is not an invitation to frivolous, bad faith attacks on patents.

As described in considerable detail below, Takeda has shown by clear and convincing evidence that Alphapharm and Mylan each filed baseless Paragraph IV certifications attacking the validity of the '777 Patent. Alphapharm's certification, which asserted invalidity due to obviousness, was deeply flawed and Alphapharm revised its theory again and again in a futile effort to state a prima facie case of obviousness. Mylan completely abandoned its Paragraph IV theory of invalidity and proceeded to trial on a contorted claim that Takeda had engaged in inequitable conduct before the Patent and Trademark Office ("PTO"). Beyond their baseless certifications, Alphapharm and Mylan each engaged in other litigation misconduct. Their misconduct was exceptional and fully justifies the award of attorneys' fees.

Legal Standard

By operation of law, Alphapharm and Mylan each infringed Takeda's patent by filing an Abbreviated New Drug Application ("ANDA") to make a generic form of pioglitazone before the expiration of Takeda's '777 Patent. 35U.S.C. § 271(e)(2). An ANDA announces the intention of the filer to produce a bioequivalent form of a drug already approved by the FDA. When

filing the ANDA the applicant must make a certification regarding any patent protecting the drug that will be copied. Both Alphapharm and Mylan chose to make a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) ("Paragraph IV"), certifying that the patent protecting pioglitazone was invalid. In making the certification, Alphapharm and Mylan were required to give Takeda notice of the " 'factual and legal basis' of invalidity." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1347 (Fed.Cir.2000) (citing to 21 U.S.C. § 355(j)(2)(B)(ii)).

An ANDA filer must "display care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity." *Id.* Such challenges are only authorized under the Hatch-Waxman Act "in accordance with strict statutory requirements" and require the challenger to state in the Paragraph IV certification that "in the opinion of the applicant *and to the best of his knowledge,* that each patent for which the applicant is seeking approval is invalid." *Id.* (citation omitted). ANDA filers are thus held to a "duty of due care" under the Hatch-Waxman Act. *Id.*

Among the remedies that are available when a patent is infringed by the filing of an ANDA is an award of attorneys' fees under 35 U.S.C. § 285 ("Section 285"), which allows the award of attorneys' fees to the prevailing party in "exceptional cases." *Id.* at § 271(e)(4). The determination of whether a case is exceptional is made by looking at the "totality of the circumstances." *Yamanouchi*, 231 F.3d at 1347 (citation omitted). In order to justify an attorneys' fees award the evidence that the case is exceptional must be "clear and convincing." *Interspiro USA, Inc. v. Figgie*

Intern. Inc., 18 F.3d 927, 933 (Fed.Cir.1994). If a case is determined to be exceptional, the decision to grant attorneys' fees is not automatic; an award should only be made when it is separately determined that it is warranted. *Id.*

Litigation misconduct that may support an "exceptional case" finding under Section 285 includes "vexatious or unjustified litigation or frivolous filings." *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1350 (Fed.Cir.2004). For example, cases that arise from the filing of an ANDA may become exceptional for purposes of Section 285"if the ANDA filer makes baseless certifications." *Yamanouchi*, 231 F.3d at 1347; *see also Glaxo Group*, 376 F.3d at 1351 (noting that "baseless accusations of invalidity" permit an award of attorneys' fees against ANDA filers). A baseless certification includes the failure "to present even a prima facie case of invalidity in filing [the] paragraph IV certification." *Glaxo Group*, 376 F.3d at 1350. The Federal Circuit has cautioned, however, that "the *mere fact that a company has filed an ANDA application or certification* cannot support a finding of willful infringement for purposes of awarding attorney's fees." *Id.* at 1350-51 (emphasis supplied). Filing a baseless Paragraph IV certification and proceeding to challenge a patent's validity despite glaring weaknesses in the theory of invalidity constitute litigation misconduct. *Id.* at 1350. Where a non-prevailing party has pursued litigation in good faith, an award of attorneys' fees is only warranted where that party has engaged in misconduct in the litigation. *See Brooks Furniture Mfg., Inc. v. Dutailier Intern. Inc.*, 393 F.3d 1378, 1381 (Fed.Cir.2005); *Forest Labs., Inc. v. Abbott Labs.*, 339 F.3d 1324, 1328-29

(Fed.Cir.2003).

Takeda's motion for an award of attorneys' fees from Alphapharm will be addressed first. This ruling presumes familiarity with the Opinion, which contains the findings of fact and conclusions of law following trial and which is incorporated by reference. Nonetheless, various terms, references and findings which are set out in detail in the Opinion are on occasion also briefly described here.

Discussion

I. Alphapharm

A. Reliance on Advice of Counsel

Before discussing the merits of the motion addressed to Alphapharm, it is necessary to determine whether Alphapharm may oppose this motion by relying on two opinions of counsel that it first produced to Takeda on April 28, 2006, with its opposition to this motion. For several reasons, it may not.

One of the opinions Alphapharm produced is a letter/memorandum dated July 12, 2003, and signed by Allen Kipnes ("Kipnes"), an attorney with the law firm Watov and Kipnes. Frommer Lawrence & Haug LLP ("Frommer"), Alphapharm' s outside counsel, retained Kipnes at the request of Generics [UK], an Alphapharm affiliate, to prepare a legal opinion regarding the validity of the '777 Patent. Kipnes reported that he and medicinal chemist Dr. Edward Glamkowski, with whom Kipnes consulted in preparing his opinion, had concluded that Takeda's previous disclo-

sure of the six-methyl compound, which is referred to as compound (b) in the Opinion and here, in both an earlier patent issued to Takeda and in an article in a scientific journal, rendered pioglitazone obvious. The prior art patent discussed by Kipnes is U.S. Patent No. 4,287,200 ("'200 Patent") and the scientific article is T. Sohda et al., *Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl] thiazolidine-2,4-dione (ADD-3878) and its Derivatives,* Chem. Pharm. Bull., 30:3580-3600 (1982) ("Sohda II"). Kipnes noted that the '200 Patent was a "broad disclosure of the claims compounds" and that Sohda II was a more specific disclosure in which compound (b) was shown to be "among a group that showed potent activity but considerable increases in body weight and fat." Kipnes took the view that based on the two disclosures, the patent examiner "should have rejected the claims of the application on prior art grounds." At trial, Alphapharm argued that the disclosure of compound (b) in these two pieces of prior art rendered pioglitazone obvious. Specifically, it asserted that the prior art identified compound (b) as a "lead" compound whose investigation would have led to the discovery of pioglitazone.

Kipnes also opined that the differences in toxicity to the liver and heart reported in Table 1 of the '777 Patent between pioglitazone and compound (b) were not surprising, and therefore were insufficient to overcome pioglitazone's prima facie obviousness. *See* Opinion at 360-62 (describing Table 1). Primarily, Kipnes questioned whether the differences between pioglitazone and the other compounds reported in Table 1 were "material" and also suggested that those reported results contradicted statements made in the

'200 Patent and Sohda II.

The second opinion Alphapharm recently produced came from Frommer attorney Jeffrey Hovden ("Hovden"). Hovden indicated that, following receipt of the Kipnes opinion, a synthetic organic chemist Dr. Ali Berkin ("Berkin"), employed by Frommer, prepared Alphapharm's Section 355 Statement under Hovden's supervision. *See* Opinion at 366-67(describing Alphapharm's Section 355 Statement).

Alphapharm was required to disclose any reliance it wished to assert in this lawsuit on advice of counsel by July 30, 2004. Because it did not disclose at that time its intent to rely on an advice of counsel defense in opposing an award of attorneys' fees to Takeda, it may not do so now.

Takeda made no secret that it would move for an award of attorneys' fees in this case. Takeda's complaint explicitly sought an award of attorneys' fees based on a finding that this case is exceptional under 35 U.S.C. § 285. On February 11, 2004, Takeda wrote to warn Alphapharm that its Paragraph IV certification, which had been filed just two weeks earlier, on January 29, 2004, appeared to have "serious omissions and errors." As explained at a conference of July 16, 2004, and as reflected in a Scheduling Order of July 20, 2004 ("July 20 Order"), the defendants' motions to bifurcate discovery and postpone their identification of and discovery concerning any advice of counsel defense were denied due to concerns re-

garding efficiency, expense, and prejudice.[2] Because the defendants had not yet identified with any clarity the issues as to which they might interpose such a defense, they were required to identify the issues on which they intended to assert an advice of counsel defense by July 30. Following such a disclosure, Takeda could demand production of documents withheld because of an assertion of privilege and take appropriate discovery. On July 30, Alphapharm notified Takeda that it would rely on advice of counsel as to the combination use patent issues only.[3]

Alphapharm also forfeited any right to rely on the Kipnes opinion when it did not identify the document on a privilege log or otherwise in response to Takeda's June 2, 2004 request for production of documents. The request included a demand for all documents concerning any opinion or advice of counsel sought or obtained by the defendants concerning the validity of the '777 Patent. Alphapharm has not given any excuse for this omission. Such an omission is wrongful, and provides an independent basis for the suppression of the Kipnes opinion.

Essentially, Alphapharm made a unilateral decision to disregard the July 20 Order and its discovery obligations, and to grant itself a bifurcation of discovery.

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[2] Alphapharm noted at the July 16 conference that it wished to preserve its right to take an interlocutory appeal from the Order, but filed no such appeal.

[3] Alphapharm later retracted that notice, and decided not to waive the privilege even as to the combination use patents. The combination use patents are for the use of pioglitazone in combination with other therapies. *See Takeda Chem. Indus., Ltd. v. Watson Pharms., Inc.*, 329 F.Supp.2d. 394, 398-99 (S.D.N.Y.2004).

Alphapharm's conduct is vexatious and constitutes litigation misconduct.

Of course, the very concerns about delay, expense and prejudice which underlay the decision to deny the motions for bifurcation are resurrected by Alphapharm's attempt at this late date to reopen discovery. Even now, Alphapharm has made only the most limited and piecemeal disclosure of its privileged documents. Takeda would not be required to take this limited production at face value, but would be entitled to disclosure of all relevant documents and an opportunity to depose witnesses to test the bona fides of this reliance defense.[4]

Alphapharm asserts that the Court's decision in January of this year, on the eve of trial summations, to take separate briefing on the issue of attorneys' fees following a ruling on the merits of the challenges to the ' 777 Patent was a decision to bifurcate discovery on the attorneys' fees issue. This argument is frivolous.[5] The briefing schedule for the attorneys'

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[4] For reasons it is unnecessary to describe here, the Kipnes opinion is deeply flawed and Takeda would have been to entitled to show that Alphapharm was well aware of that fact. Based on just the Kipnes opinion and Hovden declaration, Takeda asserts that it would have taken at least five additional depositions if the material had been produced as required in 2004.

[5] Alphapharm's similar argument that in July 2004, the Court "carved out the § 285 issues" is entirely specious. At the July 16 conference, the Court noted that the parties had been unclear on which issues they might assert an advice of counsel defense, and therefore ordered them to give notice by July 30 of every issue on which they intended to assert the defense. In giving this ruling, the Court noted that it would need a lot more information to make a judgment about efficiency and duplication of effort issues that would accompany any bifurcation, if the only issue to

fees motion in 2006 did not vacate the July 2004 Order that discovery would not be bifurcated, and Alphapharm has pointed to nothing that was said during the trial that could lead to a good faith belief that discovery would be reopened. Indeed, the motion papers filed by Alphapharm's co-defendant Mylan in opposition to this motion for an award of attorneys' fees recognizes, as they must, that Mylan cannot rely on any advice of counsel it previously received but did not disclose in 2004.

The Kipnes opinion has, in any event, very little relevance to either prong of Takeda's motion. It was obtained at least nineteen months after Alphapharm made its decision to file its Paragraph IV certification. As reported by Alphapharm, that decision had been made by November 2, 2001, at the latest; it did not obtain the Kipnes opinion until July 2003.

Similarly, Alphapharm is not in a position to rely on any work done by Berkin. Berkin is a synthetic organic chemist, and Alphapharm moved at trial, successfully, to strike the testimony of Takeda expert Dr. James Hendrickson on the ground that a synthetic organic chemist is not qualified to opine on the selection of a lead compound for further pharmacological development. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 83366 (S.D.N.Y. Jan. 11, 2006). As described in the Opinion, demon-

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which the defense was relevant was the issue of attorneys' fees. Because the defendants never indicated that the only relevant issue was their defense to a demand for attorneys' fees, and never presented the additional information necessary to support their bifurcation motion, there was no basis to bifurcate and no bifurcation even as to attorneys' fees.

strating that it would be obvious to select compound (b) as a lead compound was critical to Alphapharm's argument that the '777 Patent was invalid.[6] *See* Opinion at 375-80.

In sum, Alphapharm may not interpose an advice of counsel defense on the motion for an award of attorneys' fees. Indeed, its contention that it is entitled to do so is frivolous and vexatious.

B. Alphapharm's Paragraph IV Certification

Takeda contends that Alphapharm's January 29, 2004 Section 355 Statement was devoid of merit. Even as described in the Opinion, the Statement contained clear errors as well as arguments that Alphapharm abandoned by the time of trial. Opinion at 366-67. Viewed in its totality, Alphapharm's Section 355 Statement is so devoid of merit and so completely fails to establish a prima facie case of invalidity that it must be described as "baseless." When viewed in the context of the totality of this litigation, the filing strongly supports an award of attorneys' fees.

Despite the obvious deficiencies of its Section 355 Statement, Alphapharm points out that its Statement satisfied all of the "technical" requirements of the Hatch-Waxman Act and that it was supported by both an outside opinion of counsel and the work of three medicinal chemists and one synthetic organic chemist, and that it allowed Takeda to investigate

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[6] Alphapharm used the same argument in its effort to exclude testimony from Takeda expert Dr. Samuel Danishefsky. *See* Opinion at 373. The Court found that he was superbly qualified to opine in the field of medicinal chemistry. *Id.*

Alphapharm's claims fully. Alphapharm misses the point. The question is not whether the Statement complied with the technical requirements of the Hatch-Waxman Act, but whether the Statement breached the duty of due care that is imposed on ANDA filers by the Hatch-Waxman Act and is so devoid of merit as to be baseless.

This prong of Takeda's motion rests principally on four contentions regarding the Statement. They will be addressed in turn.

1. Selection of Compound (b) as a Lead Compound and Motivation To Optimize It Through Modifications

Takeda contends that Alphapharm's Section 355 Statement does not explain why one of ordinary skill in the art would identify a compound, identified in the Opinion as compound (b), from Sohda II (one of the two writings the Statement identified as prior art) as a lead compound worthy of further investigation.[7] This contention requires some background.

Although Alphapharm's trial presentation was characterized by a constantly shifting set of arguments, Opinion at 372 n. 37, the heart of its attack on the '777 Patent relied on the single contention that prior art compound (b) was a lead compound warranting further investigation or optimization, and that the application of two, obvious chemical processes (homologation and "walking the ring") to that compound would have led to the discovery of pioglitazone. *Id.* at 372. Thus, it was incumbent upon Alphapharm to ex-

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[7] Compound (b) from Table 1 of the '777 Patent was compound 58 in Sohda II.

plain in its Statement what in the prior art would have led one skilled in the art to identify compound (b) as a lead compound. For the reasons explained in detail in the Opinion, the evidence at trial showed that one skilled in the art would certainly not have concluded that compound (b) should be chosen as a lead compound over the many other more obvious or at the very least similarly interesting choices presented by that prior art. Indeed, Sohda II teaches away from compound (b) when it specifically comments on its negative effects on body weight and brown fat. Opinion at 377.

Despite the centrality of compound (b) to Alphapharm's trial strategy, and the herculean efforts that its trial expert made to explain despite all the evidence to the contrary why Sohda II would lead one skilled in the art to identify compound (b) as a lead compound, *see id.* at 377-78, the Statement did not even make that argument.[8] The Statement focused instead on two other compounds described in Sohda II, which the Statement then misidentified, *see id.* at 36-67, as described below. As a consequence, Alphapharm's Statement did not grapple with the many

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[8] The Statement does not identify compound (b) as a lead compound. It merely observes that compound (b) was one of several compounds related to pioglitazone that were specifically mentioned in the '200 Patent as an example of the patented formula that has shown both low toxicity and efficacy in mice. The Statement then asserts that "the specific disclosure of [compound (b)] as described in the '200 Patent and [Sohda II] render [sic] the claimed compounds of the '777 patent, including pioglitazone, obvious and therefore unpatentable." There is no explanation for why compound (b) would have stood out from all the other compounds not related to pioglitazone or, for that matter, to the other compounds related to pioglitazone.

impediments evident in Sohda II for choosing compound (b) as a lead compound. In this regard, it is noteworthy that Dr. Howard Rosenberg ("Rosenberg"), the head of Alphapharm's intellectual property department, a medicinal chemist, and an Alphapharm officer who assisted in formulating the Statement, admitted in his deposition that there was "nothing" to recommend compound (b) over several other compounds, and he only chose it as a lead compound "because it was similar to pioglitazone." *Id.* at 377. This is a stunning admission that Alphapharm worked backwards from pioglitazone's success to identify what it would contend was a "lead" compound, and relied exclusively on hindsight.[9]

Alphapharm contends in opposition to this motion that Rosenberg did not impermissibly rely on hindsight, but explained in his deposition that compound (b) was identified by Alphapharm as a lead compound because the data presented in Sohda II showed that it was one of seven active compounds. It also asserts that Rosenberg only received the Statement in its final form after it had been filed. But, this analysis of the compound's activity did *not* appear in the Statement either. In any event, this iteration of Alphapharm's argument is also scientifically worthless.

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[9] Even in opposition to this motion, Alphapharm improperly depends on post-hoc reasoning. It contends that it was obvious to identify compound (b) as a lead compound since it is a homolog of a compound covered by the '777 Patent, although not a homolog of pioglitazone. Alphapharm relies on the asserted legal principle that homologs are presumed to be *prima facie* obvious. This can not explain, however, why compound (b) would have been identified by one skilled in the art as a compound worthy of further investigation.

Sohda II identified three compounds, and not compound (b), as having the most favorable performance. As for the seven compounds with the highest efficacy scores, six of the seven, including compound (b), were identified as having problems with either toxicity or side effects. *See* Opinion at 376. Sohda II simply does not support the selection of compound (b) as a lead compound. Moreover, whether Rosenberg saw the finalized Statement before its filing is quite beside the point since, as he admitted in his deposition, he "formulated" the opinion of invalidity on which Alphapharm's Statement was premised.

Alphapharm's Statement is similarly deficient in its explanation of why one skilled in the art would be motivated to modify compound (b) in a way that would lead to the discovery of pioglitazone. In making the argument that one skilled in the art would have learned from Sohda II that an ethyl and methyl are "equivalent with respect to biological activity on a closely related analog of pioglitazone," the Statement misidentified the compounds as having pyridyl rings at their left moeity, while they in fact had benzene rings.[10] *Id.* at 366-67. While Alphapharm in opposition to this motion asks this Court to find that this error was due to mere sloppiness, in fact the error is more insidious. It underscores that Alphapharm was grasping at straws, and did not act with due care or in good faith.

Alphapharm points out that its expert at trial, Dr. Henry Mosberg ("Mosberg"), referred to these same two misidentified compounds-compounds 11 and 14

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[10] A benzene ring, in contrast to phenyl ring, does not have a nitrogen atom. Opinion at 382 n. 66.

from Sohda II-as examples of routine methyl-ethyl substitution or homologation.[11] But, there is no discernable pattern of biological activity associated in a comparison of the many compounds listed in Sohda II as having either a methyl or ethyl substituent.[12] Nothing in the prior art suggests that substituting an ethyl for a methyl would be of any more assistance in improving a compound's toxicity or efficacy profile than using any of the other many possible substituents or than changing course entirely and adopting a different parent structure. *See* Opinion at 383. Indeed, a careful reading of Sohda II would lead one skilled in the art to conclude that homologation had no tendency to decrease unwanted side effects. *Id.* In any event, Alphapharm is mischaracterizing Mosberg's testimony. Mosberg admitted that one of ordinary skill could not use compounds 11 and 14 to predict or extrapolate the effect of homologation to a pyridyl compound. As the trial evidence made abundantly clear, the very best that Mosberg could offer was his opinion that biological activity is unpredictable and it would have been obvious to try homologation. This is a far cry from evidence that one skilled in the art would have had any reasonable basis to expect success from homologation. *Id.* at 384-85.

The Statement was required at a minimum to outline the basis for choosing compound (b) as a lead compound and for modifying it in the ways proposed by

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[11] An ethyl group, C_2H_5, differs from a methyl, CH_3, by a single CH_2 group. They are homologs since they differ from each other through the addition of a repeating group, the single CH_2 group.

[12] The term substituent is used in chemistry to describe an atom or group of atoms that is substituted in place of a hydrogen atom.

Alphapharm at trial. It did not do so. The Statement was critically deficient as a result of these failures.

2. Comparison with Ciglitazone

Takeda asserts that the Statement erred when it asserted (1) that Takeda did not demonstrate that pioglitazone was surprisingly superior to another molecule-ciglitazone[13]-and (2) that the '777 Patent disclosed an entirely different activity for ciglitazone than was disclosed in the prior art. Alphapharm's Statement contrasts the toxicity of ciglitazone reported in Table 1 of the '777 Patent, where it is described as toxic, and in the prior art, where it is described as having low toxicity. The Statement then observes:

> *The Applicant of the '777 patent did not explain the contradiction between its application and its prior art disclosure.* The prior art undermined the Applicant's conclusion that the data presented in Table 1 actually showed that pioglitazone had surprising or superior toxicity level. (Emphasis supplied.)

The Statement makes largely the same observation in the context of comparing the efficacy of pioglita-

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[13] Takeda discovered the first thiazolidinedione ("TZD") compounds in the 1970s. By the 1990s, the introduction of TZD pharmaceuticals had revolutionized the treatment of diabetes by enhancing the muscles' ability to take glucose from the blood stream. Opinion at 347. Takeda synthesized the TZD ciglitazone in 1978, and worked many years to develop it, until it was abandoned during human clinical trials as toxic. *Id.* at 349. Thereafter, Takeda searched for a compound that was both more potent than ciglitazone and non-toxic. *Id.*

zone and ciglitazone as presented in the '777 Patent and in the prior art.

These assertions in Alphapharm's Statement were baseless. Alphapharm's Rosenberg admitted that pioglitazone is "clearly superior" because it is non-toxic. Opinion at 385. It is also undisputed that pioglitazone is far more potent than ciglitazone. *Id.* at 358. One skilled in the art who read the ' 777 Patent and the prior art would have concluded that the '777 Patent demonstrated pioglitazone's superiority over ciglitazone and would not have found any contradiction in the differences in the descriptions of ciglitazone's toxicity when it is compared to different groups of compounds. In brief, ciglitazone had low toxicity when compared to other compounds analyzed at the time of Sohda II but was far more toxic than pioglitazone.

Alphapharm's concedes that it abandoned these arguments at trial, noting that it chose to focus on other concerns with Takeda's data.[14] These arguments from its Section 355 Statement were abandoned because they were unsupportable, not because Alphapharm made a tactical decision regarding which argument should be emphasized at trial.

3. Table 1's Evidence of Pioglitazone's Superiority

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[14] To the extent that Alphapharm tries to explain its abandonment of these arguments by the time restrictions imposed at trial, that excuse is entirely frivolous. There was no limitation imposed on any party in the presentation of its witnesses' direct testimony and none of Alphapharm's experts pressed this point. Nor did Alphapharm contend at trial that it wished to make this argument but could not because of time restrictions.

Takeda asserts that Alphapharm's Statement erred when it represented that Table 1 of the '777 Patent does not show the superiority of pioglitazone. As it had done in its discussion of ciglitazone, the Statement compared earlier statements in the prior art describing certain compounds as non-toxic and briefly analyzed the statistical significance levels reported by Takeda in Table 1 to conclude that the "prior art undermined the conclusion that the data presented in Table 1 of the '777 Patent actually showed that pioglitazone had surprising or superior toxicity levels." The Statement went on to point out that several of the comparison compounds had similar (and in the case of one compound superior) efficacy scores to that reported for pioglitazone in Table 1. The Statement concluded that

> The similar, or in fact superior activity of the reference compounds coupled with the lack of support of surprising results in the toxicity tests supports the conclusion that *whatever credible differences may have been presented in the '777 patent were insufficient to overcome the prima facie case of obviousness.*

Alphapharm has not responded to Takeda's contention that an award of attorneys' fees is appropriate because Alphapharm's statement made a baseless claim that the '777 Patent did not show pioglitazone's superiority. At trial, Alphapharm did not reassert this analysis from its Statement, and for good reason. As already noted above, Alphapharm's Rosenberg admitted that pioglitazone was "clearly superior" to compound (b) because of the latter's toxicity. Takeda

is correct that the Statement was seriously deficient in this regard as well.

4. Secondary Indicia of Non-Obviousness

Takeda asserts that the Statement is deficient because it did not address sufficiently the secondary indicia of non-obviousness, such as the commercial success of Actos®, the brand name for the compound containing pioglitazone. Alphapharm responds that it could not address secondary considerations relevant to the issue of obviousness in its Statement since none of the information relevant to those considerations was in Alphapharm's possession at the time the Statement was drafted and it required discovery of Takeda. In particular, it contends that it could not comment on the substantial commercial success of Actos® without obtaining information about the marketing of the drug, and Takeda's profits and forecasts. The most important fact concerning non-obviousness, the significant commercial success of Actos®, was well known to Alphapharm and required no discovery. The Statement was deficient in this regard as well.

In sum, several of the deficiencies Takeda has identified in Alphapharm's Statement are so glaring that, by themselves, they defeat any assertion that the Statement gave adequate notice of the factual basis of invalidity, was drafted with due care, or presented a prima facie case for invalidity due to obviousness.[15] Considered together they highlight that Alphapharm

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[15] This is particularly apparent because, as Alphapharm's Statement acknowledges, it had to prove its case by clear and convincing evidence. *See* Opinion at 371.

not only abrogated the duty of due care to which ANDA filers are held but acted in bad faith in filing its Paragraph IV certification.

C. Alphapharm's Litigation Misconduct

Takeda also asserts that this is an exceptional case because Alphapharm engaged in litigation misconduct following the filing of its Section 355 Statement. It asserts first that Alphapharm largely abandoned the articulation of obviousness in its Section 355 Statement, and presented an ever-shifting collage of arguments in a futile search for a coherent theory of obviousness. Second, without any reasonable basis and in bad faith, Alphapharm attempted at trial to convert its attack on the '777 Patent into an inequitable conduct claim. Third, as already discussed, in response to this motion, Alphapharm ignored the July 20 Order and offered an untimely advice of counsel defense.

1. Alphapharm's Search for a Theory of Obviousness

Some of the highlights in the evolution of Alphapharm's obviousness argument are as follows. As already described, Alphapharm's Rosenberg used hindsight at his deposition to explain why compound (b) would have been selected as a lead compound. That deposition occurred on March 18 and March 30, 2005. Essentially, Rosenberg identified ten lead compounds that could be identified from the prior art and several categories of substituents that it would be

useful to test to compare biological activity.[16] This protocol would have required the testing of hundreds of lead compounds and could not be the basis of a challenge to the '777 Patent based on obviousness.

Barry Spencer ("Spencer") was Alphapharm's 30(b)(6) witness, and testified on May 5 and 6, 2005. He presented a complex roadmap that he asserted would have led one skilled in the art to identify two compounds as lead compounds, compound (b) being one of the two. This was an entirely different analysis than laid out in the Statement or described by Rosenberg, who had contributed to the drafting of the Statement. Using biological activity data from Sohda II, Spencer identified thirty-six compounds of interest, and added a thirty-seventh recommended by the author of Sohda II. Purporting to use information from Sohda II about toxicity and side effects, he narrowed the list to twenty-six. Then, using a 1980 declaration from Takeda employee and co-inventor on the '777 Patent Dr. Takeshi Fujita ("Fujita") filed in connection with an earlier Takeda patent, he narrowed the list to three. Alphapharm's Statement, however, had not identified this declaration as prior art. In any event, Spencer then eliminated one of the three because the data in the prior art indicated that it had a lower efficacy index than ciglitazone.[17]

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[16] Rosenberg identified chorides, halides and CF_3 as substitutuents to test, but did not identify ethyls. Pioglitazone has an ethyl substituent at its left moeity, the end of the compound at issue here.

[17] Spencer had no response when confronted at his deposition with the passage in Sodha II that warned of negative side effects generated by compound (b). He simply acknowledged the passage but continued to insist that compound (b) would be one of

Within two months of Spencer's deposition, Alphapharm changed course again. On July 15, 2005, it served Mosberg's expert report. Mosberg identified yet new sources of prior art: two other Takeda patents, the '779 and '605 patents, and their file histories. Based on the prior art, Mosberg posited that one skilled in the art would have identified compound (b) as a lead compound. Mosberg asserted that one skilled in the art would also have engaged in two steps to alter compound (b) and create pioglitazone: homologation and then walking the ethylated compound around the pyridyl ring that lies at the left moeity of the compound. A description of these processes can be found in the Opinion at 381-85. Mosberg did not point to anything from the prior art, however, to support a reasonable belief that the homologation and ring walking would improve a compound's efficacy and toxicity profiles. As Mosberg's notes, introduced at trial, showed, all he could assert was that these processes were "obvious to try". *Id.* at 384. Even at trial, the best that he could offer was that anything can happen when one modifies a compound, so a change for the better would not be surprising. *Id.* at 385.

Then, at his deposition on September 19 and 20, 2005, Mosberg asserted that one skilled in the art would have investigated all 2-pyridyl, 3-pyridyl, and to a lesser extent 4-pyridyl compounds.[18] Pioglitazone

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the compounds that would have been selected for further development.

[18] The number indicates the position at which the pyridyl ring is attached to the body of the molecule, counting from the highest atomic weight atom in the ring and moving counter-clockwise.

is a 2-pyridyl compound.

At trial, Mosberg again relied on the '779 patent[19] and identified compound (b) as a lead compound. When confronted with the many problems associated with the identification of compound (b) as a lead compound based on the prior art, Mosberg turned the identification of a lead compound on its head. He asserted, without any analytical or scientific support, that one skilled in the art would have selected compound (b) for further investigation because the prior art indicated that Takeda was *not* actively pursuing it, and Takeda would have had an advantage in the development of those compounds in which it had a head start. *Id.* at 377.

Alphapharm's response to this damning recitation of its ever-evolving theory of obviousness underscores its bad faith. It excuses Spencer's testimony on the ground that he is not a medicinal chemist and testified before Alphapharm had retained Mosberg. It characterizes the differences between Spencer's analysis and Mosberg's as "slight", when they are enormous. Finally, it justifies at least some of Mosberg's innovations on the ground that they should not have been surprising to Takeda.[20]

As for the iterations of its obviousness claim pre-

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[19] Takeda suggests that Mosberg relied on both the '779 and '605 patents at trial, but the '605 patent is not mentioned in his trial declaration. Alphapharm nonetheless repeatedly relied on the '605 patent, identifying it as one of six pieces of prior art in its opening trial memorandum.

[20] In this connection, Alphapharm refers to evidence provided by Dr. Douglas Morton from The Upjohn Company, Takeda's research partner in the development of pioglitazone.

sented at trial, Alphapharm does not grapple with its utter failure to show why compound (b) would be selected as a lead compound. Instead, it now contends that the identification of a lead compound is simply not a part of the obviousness analysis since (1) pioglitazone is closely related to compound (b), which was disclosed in the prior art, and (2) closely related compounds are presumed to have similar properties and are considered prima facie obvious over the prior art. With this argument, Alphapharm essentially concedes that the many contradictory justifications presented in its Section 355 Statement and by its witnesses for the selection of compound (b) as a lead compound were utterly indefensible and fatally flawed.

Instead of defending the selection of compound (b) as a lead compound whose investigation would have led to the discovery of pioglitazone, Alphapharm asserts simply that the Manual of Patent Examining Procedure ("MPEP") allows a presumption that homologs have similar properties, and then tries to explain why the data presented by Takeda in Table 1 of the '777 Patent-data which shows the superiority of pioglitazone-were insufficient to rebut the presumption. *See* U.S. Patent & Trademark Office, Manual of Patent Examining Procedure, § 2144.09 (8th ed.2001). To do this, Alphapharm makes an entirely misleading presentation.

Alphapharm's brief in opposition to this motion contains a chart with quotations from three Takeda patents that preceded the '777 Patent. The quotations

refer to TZDs[21] as a class and assert that they have low toxicity. The chart presents the statements, however, as if they represent a relative assessment of compound (b)'s toxicity profile. As explained in the Opinion, however, the facts laid out in Table 1 are to the contrary. Compound (b) is quite toxic, a fact that underscores the unexpectedness in the discovery of pioglitazone's nontoxicity. Opinion at 385. Again, Rosenberg admitted in his deposition that pioglitazone is clearly superior to the closest prior art, and that Table 1 of the '777 Patent established that clear superiority. It was improper of Alphapharm to continue to contest that issue after Rosenberg's deposition, and it is doubly wrongful for it to make that misleading argument at this late stage.

In any event, Alphapharm's legal analysis is flat wrong. The law requires Alphapharm to show that the prior art gave a reason or motivation to make the claimed composition. Opinion at 371 (citing *Yamanouchi,* 231 F.3d at 1343). As an initial matter, one must identify a lead compound that one skilled in the art would be motivated to modify. Alphapharm was never able to defend its identification of compound (b) as a lead compound. Moreover, the MPEP itself cautions against equating homology with prima facie obviousness. MPEP at § 2144.09.

Alphapharm similarly misrepresents Mosberg's testimony about the expectations that one skilled in the art would reasonably have from applying the processes of homologation and ring walking to compound (b). Relying on quotations from Mosberg's expert re-

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[21] TZD's are a class of compounds developed by Takeda for treating diabetes. *See* Opinion at 347. Pioglitazone is a TZD.

port and trial declaration,[22] Alphapharm contends in opposition to this motion that Mosberg opined that a skilled artisan would have had a reasonable expectation of successfully obtaining a better drug albeit not necessarily a blockbuster drug. First, no one but Alphapharm has suggested that the relevant test is an expectation of a discovery of a blockbuster drug. Second, Alphapharm has simply ignored Mosberg's many concessions in his writings, and deposition and trial testimony that entirely eviscerate the formulations in his report and declaration. These include his acknowledgment that the biological effects of various substituents are unpredictable and that improvements in efficacy and toxicity profiles from homologation and ring walking were neither expected nor unexpected. Opinion at 384-85 and n. 74. By summation, Alphapharm's counsel could do little to cabin the damage done by Mosberg's trial testimony, and argued simply that an improvement in a compound's profile would not be surprising. *Id.* at 385. That, of course, falls far short of evidence of a reasonable expectation of success.

Alphapharm had over two years between the time it decided to file a Paragraph IV certification and its filing of its Statement. The assertion of obviousness in a Section 355 Statement must be rooted in an analysis of prior art and made with due care. Alphapharm was still searching for a viable theory at trial. It has utterly failed to explain why its Statement was so flawed and why its description of obviousness went through such a dramatic evolution between the filing of the Statement and trial. The evidence of Al-

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[22] The trial witnesses presented their direct testimony through affidavits or declarations. Opinion at 344.

phapharm's bad faith is overwhelming.

2. Alphapharm's Assertions of Inequitable Conduct

At trial, Alphapharm asserted several arguments of little relevance to its claim of obviousness. They are best understood as assertions that Takeda engaged in inequitable conduct. Because Alphapharm had not pleaded an inequitable conduct claim, Alphapharm's attempts to insert these new issues created confusion, wasted valuable court time, and increased the burden of the litigation on the parties.

First, in its proposed findings of fact, Alphapharm contended that Takeda presented unreliable data on toxicity to the PTO in the prosecution of the ' 777 Patent. It then moved to preclude Takeda's toxicology expert from explaining that Alphapharm's assertion was misleading and false. Alphapharm's assertion that the data on toxicity presented to the PTO by Takeda in the ' 777 Patent could not be replicated and was unreliable rested on test results that only became available *five years* after the '777 Patent was issued. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 137374, *3 (S.D.N.Y. Jan. 11, 2006). This argument was entirely frivolous.

Then, at trial Alphapharm appeared to be fashioning an inequitable conduct argument through a comparison of the toxicity data Takeda provided to the PTO for the '777 Patent, and general statements in a prior Takeda patent application about toxicity levels found in TZDs. The comparison was spurious. Opinion at 379 n. 58.

Finally, in summation, Alphapharm added yet another new argument. The argument focused on the requirement that a patent contain a description (also called a specification) of the claimed invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same." 35 U.S.C. § 112. As Alphapharm has had to concede, however, it did not choose to challenge the '777 Patent based on the adequacy of the specification and this argument was a red herring. The sole challenge brought by Alphapharm was whether the '777 Patent was obvious over the prior art and on this question its legal argument was not as persuasive as Mosberg's own handwritten notes agreeing with Danishefsky's view that based on the prior art, the impact of even small changes in a chemical compound on biological activity was unpredictable. Opinion at 384.

In sum, Alphapharm's arguments that Takeda engaged in inequitable conduct were entirely frivolous. The arguments cannot be excused as mere comment of the credibility of Takeda's witnesses, an argument that Alphapharm makes in opposition to this motion. What Alphapharm's inequitable conduct arguments underscore is that it had lost all confidence in its claim of obviousness, and was grasping at straws. This conduct further supports the award of attorneys' fees.

D. Totality of Circumstances

Alphapharm contends that in deciding whether this is an exceptional case warranting the award of attorneys' fees, the Court should weigh the closeness of

the case, the conduct of the parties,[23] and the tactics of all counsel. Weighing these factors does not assist Alphapharm.

This case was not close. Alphapharm's evidence fell woefully short of demonstrating a credible claim of obviousness. The claim of obviousness was asserted without due care and prosecuted in bad faith. As already demonstrated, Alphapharm's conduct of the litigation and tactics were deeply flawed.

Alphapharm identifies a few specific factors to weigh in its favor. It contends that Mosberg's reliance on the '605 and '779 patents as relevant prior art, references which were not disclosed in its Section 355 Statement, was an appropriate response to Takeda's contention that Sohda II taught away from compound (b) as a lead compound. The fact that Sohda II taught away from compound (b), however, was not news.[24] The Statement did not even identify compound (b) as a compound of interest disclosed in Sohda II. To the extent that the '605 and '779 patents provided any support for the selection of compound (b) as a lead compound, then Alphapharm was under an obligation to identify these two references in its Statement.

Alphapharm contends that it "took steps at every

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[23] Alphapharm has raised only one claim that Takeda engaged in misconduct in defending the '777 Patent. In a footnote, Alphapharm faults Takeda for raising issues concerning the '902 patent for the first time at trial.

[24] Sohda II identified three compounds, none of which was compound (b), as exhibiting the most favorable properties in terms of activity and toxicity. It warned that compound (b) caused considerable increases in body weight and brown fat. Opinion at 375-76.

juncture to simplify the issues" for trial, pointing to its consent to the severance of the trial of the claims associated with the combination use patents, its completion of fact discovery during the time allowed, its withdrawal of its jury demand, its reduced request for time to present its case at trial,[25] and its use of only two experts. Alphapharm has not shown, however, that these decisions were anything other than decisions taken in its own interest and/or decisions as to which it had no viable alternative. In any event, they are insufficient when weighed against the other evidence of misconduct described in this Opinion to prevent an award of attorneys' fees.

Alphapharm also asserts that attorneys' fees should not be awarded because it relied upon a well respected and experienced medicinal chemist, Mosberg. Actually, Alphapharm did not rely on Mosberg's analysis until the time of the trial. Mosberg had no role in the formulation of the Statement or in the presentations made by Rosenberg and Spencer. Mosberg's analysis of obviousness was eviscerated at his deposition and trial. Indeed, in opposing this motion, Alphapharm does not rely on Mosberg's explanation of why compound (b) would have been seen by one skilled in the art as a lead compound, relying instead on Rosenberg's analysis, which was also thoroughly discredited at trial. As for the second prong of Mosberg's testimony, his explanation as to why one skilled in the art would have been motivated to apply homologation and ring walking to compound (b) in order to optimize the molecule, during summation Alphapharm's counsel struggled to limit the damage

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[25] Alphapharm notes that it reduced its request to two days, which the Court further reduced to eight hours.

done by Mosberg's testimony on these issues as well. *See* Opinion at 385.

In contrast to the defendants, Takeda brought to the trial scientists of extraordinary accomplishment and distinction who took the time they needed to study the issues thoroughly and to develop their analyses. *See* Opinion at 373 n. 39. While Mosberg is certainly a respected and experienced medicinal chemist, for whatever reason he did not devote the care and attention to this assignment that it deserved. As a result, he delivered a series of opinions that were completely undercut by a careful examination of the prior art and the application of sound science. Alphapharm must bear the responsibility for this and cannot avoid the imposition of sanctions by hiding behind Mosberg's resume.

In sum, Takeda is entitled to an award of attorneys' fees from Alphapharm. Alphapharm's Section 355 Statement was deeply flawed, filed in bad faith, and fails to present even a prima facie case of invalidity. Alphapharma made these proceedings far more complex and expensive by constantly shifting its theory of obviousness in a futile effort to locate a coherent argument. Even in response to this motion, it has misrepresented the record in this litigation. This is the exceptional case where an examination of the totality of the circumstances amply justifies, indeed compels, the award of attorneys' fees.

II. Mylan

Takeda has moved for as award of attorneys' fees against Mylan for filing a Paragraph IV certification

in bad faith and for litigation misconduct following the close of fact discovery. Mylan abandoned in its entirety its claim of obviousness contained in its Section 355 Statement, and then after the close of discovery propounded a frivolous claim of inequitable conduct. These, and the other grounds pressed in Takeda's motion, are detailed below.

A. Mylan's Obviousness Claim

Mylan filed a Paragraph IV certification in bad faith and with no reasonable basis to claim that the '777 Patent was invalid. Its Section 355 Statement was deeply flawed and never defended during discovery. Mylan then engaged in further misconduct, attempting to substitute a new theory of obviousness following the close of fact discovery. The Court rejected Mylan's attempt to alter its theory of obviousness at that late stage. Mylan's misconduct was exceptional and deserves the imposition of sanctions.

Mylan decided to challenge the validity of the '777 Patent without any good faith basis to do so. The relevant facts are as follows. Even though it had not yet obtained an opinion to support a Paragraph IV certification, Mylan stationed a person outside the FDA office on May 27, 2003, over six weeks prior to July 15, the first day it could file an ANDA, intending to have a "line stander" hold its place on a 24/7 basis.[26] Mylan had retained the law firm of Foley Hoag, LLP as of April 2003 to analyze the '777 Patent, but the firm was unable to provide an opinion of invalidity by July 15. With July 15 swiftly approaching, on

[26] The FDA demanded that Mylan's line-stander leave the premises.

July 11, Mylan hired Levy & Grandinetti, a two person law firm, to prepare an opinion, and the firm did so after just sixteen hours of work. Mylan did not produce that opinion during the course of this litigation. With the opinion in hand, it made its ANDA filing on July 15, and then returned to Foley Hoag, which completed its work in August. Foley Hoag was not responsible for preparing Mylan's Section 355 Statement, however, and its August opinion was not produced in this litigation either. Instead, Mylan retained its trial counsel, Cohen, Pontani, Lieberman & Pavane, to prepare its Statement, which was filed on September 8, 2003. Within five weeks, on October 13, Takeda warned Mylan that its certification lacked merit and was an abuse of the statute and the rules.

Mylan's Section 355 Statement identified two pieces of prior art, the '200 Patent and Sohda II. It argued that one compound with a benzene ring at its left moeity made the invention of pioglitazone obvious. (The pioglitazone molecule had a pyridyl ring, not a benzene ring, at its left-moiety.) Mylan misdescribed the benzene compound's structural relationship to pioglitazone and its efficacy as disclosed in Sohda II. Opinion at 367-68. It also gave no reason to select the compound as a lead compound warranting further investigation and optimization.

Mylan resisted discovery of its theory of obviousness, and then when again ordered by the Court after the close of fact discovery to do so, it gave notice that it had abandoned the theory of obviousness set forth in the Statement. *See Takeda Chem. Indus. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2005 WL 2092920, *1 (S.D.N.Y. Aug. 31, 2005); *Takeda Chem. Indus. v. My-*

lan Labs., Inc., 03 Civ. 8253(DLC) (S.D.N.Y. entered on June 21, 2005) (Memorandum Opinion and Order limiting Mylan's presentation of evidence at trial to theories set forth in September 8, 2003 Notice). In its stead, Mylan sought to substitute a new theory of obviousness based on a different compound mentioned in Sohda II. The Mylan Statement had focused on compound 14; Mylan's new theory focused on compound 57 (which was described at trial as compound 3894, a compound that had an unsubstituted pyridyl ring as its left moeity). Mylan did not give any detailed explanation of why compound 57 would have been identified by one skilled in the art as a lead compound, or how its optimization would have led to the discovery of pioglitazone. This theory was also advanced in bad faith: Mylan's 30(b)(6) witness had just days earlier indicated that an analysis of the toxicity and efficacy profile of compound 57 would have ruled it out as a lead compound.

In an Order entered on June 21, 2005, Takeda's motion to preclude Mylan from asserting this revised theory of obviousness was granted. Mylan then moved for reconsideration, inappropriately raising several new arguments and making legal arguments that were absolutely frivolous. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 2005 WL 2092920, *4. The motion for reconsideration was denied on August 31, 2005. *Id.* at *6.

Mylan's defense to this prong of the motion for sanctions is entirely unpersuasive. Mylan asserts that it did not need a good faith basis to have a line-stander, and argues that Takeda is drawing an impermissible negative inference regarding the advice Mylan re-

ceived from counsel even though Mylan has elected to rely on its right to withhold the opinions as privileged. *See Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337, 1344-45 (Fed.Cir.2004) (en banc).

Mylan also asserts that it is not required to obtain advice from outside counsel so long as it has another basis for a *bona fide* belief that the '777 Patent was invalid. Mylan asserts that it relied on its in-house patent attorney Shelly Monteleone, who customarily consults with both outside counsel and Mylan scientists before deciding whether an ANDA could be filed. The problem with its assertion of reliance on Monteleone, however, is that she testified that she had no recollection of actually doing any work on the pioglitazone project and could only testify as to her customary practices.

An adverse inference may not be drawn against Mylan for its failure to present an opinion from counsel that could establish its *bona fides* in filing an ANDA and then its Statement. Without relying on any such inference, however, Takeda has carried its burden of showing that Mylan did not act with due care or in good faith.

As for the substance of its Section 355 Statement, Mylan asserts that it should not be judged against the standard of success at trial, that is, whether it had clear and convincing evidence of obviousness, but rather whether it had "a reasonable basis" for asserting that one skilled in the art "would be interested in compound 14." Mylan relies on its characterization of compound 14 and pioglitazone as "non-classical bioi-

sosteres", and a purported presumption that compounds that are so related have broadly similar biological properties, automatically rendering pioglitazone obvious in Mylan's view. Mylan points out that, in any event, it dropped the claim, and the mere fact that it had pleaded it does not constitute vexatious litigation.

This defense of the merits of its Section 355 Statement is utterly frivolous, and is further evidence that an award of attorneys' fees against Mylan is appropriate. Sohda II described 101 specific TZD compounds, giving data on each compound's efficacy. Opinion at 350-53. Mylan has never presented any explanation for why one skilled in the art would single out compound 14 in Sohda II as a lead compound warranting further investigation. Mylan's 30(b)(6) witness could not identify any basis to differentiate the compound from the many others that the article described as performing better or as well as it did. Moreover, Mylan has never presented any expert testimony to support its theory that the compound is a bioisostere of pioglitazone. In contrast, Takeda's distinguished expert explained in his expert report that it is not. In any event, neither Mylan's Section 355 Statement, nor its opposition to this motion, present any explanation of why one skilled in the art would have been motivated to make the substantial modifications to compound 14, which has a benzene moeity, to arrive at pioglitazone, which has a pyridyl moeity at its left end.

Finally, Mylan attributes its delay in identifying its second theory of obviousness on Takeda's delay in producing an unredacted version of internal Takeda

report A-15-34. *See* Opinion at 357-58. According to Mylan, the document disclosed that compound 57 (a/k/a compound 3894) had comparable activity and "only slightly greater toxicity" than pioglitazone. It points out that Takeda was not burdened by Mylan's assertion of this revised theory of obviousness since the Court precluded Mylan from asserting it at trial. Mylan contends that its motion for reconsideration was justified since the Court had overlooked the issue of prejudice as articulated in *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed.Cir.1998). As was explained in the decision denying Mylan's motion for reconsideration, *Lydall* does not require a finding that Takeda had been prejudiced to preclude Mylan's last-ditch obviousness theory, but even if it were necessary to find prejudice, there was ample evidence that Takeda had been prejudiced. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 2005 WL 2092920, *5-6.

Mylan's defense of its aborted effort to make a wholesale revision to its obviousness theory is utterly frivolous. As this Court has previously had occasion to point out to Mylan, *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 2005 WL 2092920, at *4, since an attack based on obviousness must rely on disclosures made in prior art, the existence or receipt of Takeda's internal documents is irrelevant. Either the invention of pioglitazone was obvious based on prior art, or it was not. It is also extremely misleading of Mylan to characterize compound 3894 as having only slightly greater toxicity than pioglitazone. Compound 3894 was disqualified by Takeda and Upjohn from further consideration in the Fall of 1984 because of its toxicity to the heart. Opinion at 397. Toxicity was of paramount concern to the two companies as they se-

lected the handful of compounds into which they would be investing considerable resources. *Id.* at 358-59. In contrast to compound 3894, pioglitazone met the companies' toxicity criteria. *Id.* at 359.

In sum, Mylan's ANDA filing and Statement were baseless and filed in bad faith. On this ground alone, Takeda would be entitled to an award of attorneys' fees.

B. Mylan's Litigation Misconduct Associated with Pursuit of an Inequitable Conduct Claim

Takeda also moves for an award of attorneys' fees on the grounds that Mylan (1) did not have a good faith basis for its inequitable misconduct claim; (2) wrongfully delayed disclosing the claim in order to prejudice Takeda; (3) was unable to identify any material misstatement in Takeda's application for the '777 Patent; (4) relied on Dr. Lawrence Hendry ("Hendry") as an expert for issues on which he was not qualified to opine, *see Takeda Chem. Indus. v. Mylan Labs., Inc.,* 03 Civ. 8253(DLC), 2006 WL 44053 (S.D.N.Y. Jan. 9, 2006)(granting in part Takeda's *motion in limine*); (5) frivolously asserted that Takeda had suppressed evidence that pioglitazone was toxic to the liver; (6) asserted that compound 3894 was the closest prior art when it knew it was not; and (7) lacked any theory or evidence of Takeda's intent to mislead the PTO. Mylan responds to only some of these issues. It presents no defense directed specifically to items 4, 5 and 6.

Before analyzing these issues, a brief description of Mylan's claim of inequitable conduct is in order. My-

lan's theory of inequitable conduct was cobbled together from arguments addressed principally to two compounds, one of whose test results were reported by Takeda on Table 1 of the '777 Patent, and one whose results were not. Opinion at 390. Mylan argued that Takeda misrepresented the data regarding compound (c)'s potency in order to make it appear that the compound was weaker than pioglitazone. There were a host of problems with this theory, including the fact that Takeda had evidence that compound (c) had failed the chick lens assay test and had therefore been categorically eliminated as a candidate for development because of its toxicity. *Id.* at n. 82.Therefore, whatever its efficacy, pioglitazone could easily be shown as superior to compound (c). With respect to compound 3894, whose test results Takeda did not present to the PTO, Mylan argued that it was the closest prior art to pioglitazone, and that Takeda had a duty to disclose its performance in tests to the PTO. This theory was also fatally flawed for many separate reasons, including the fact that compound 3894 was not the closest prior art, that Takeda had no duty to present the PTO with information about the compound, and that in any event it had been rejected for development by Takeda due to its toxicity to the heart.

Proof of wrongful intent is of course a necessary component of an inequitable conduct claim. *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1128 (Fed.Cir.2006); Opinion at 387-88. Mylan never had any evidence of wrongful intent by Takeda, and despite promises at trial that it would produce some, utterly failed to do so. In contrast, there was powerful, irrefutable evidence that Takeda acted with com-

plete integrity in its dealings with the PTO. Opinion at 389-90, 398-99. Among other things, when it made its application to the PTO it presented the very test results upon which it and Upjohn had relied internally in making their joint selection of the compounds into which they would invest further research resources to try to develop a pharmaceutical. *Id.* at 389, 398.

As for Mylan's delay in asserting this claim, Mylan waited until the end of the period for fact discovery to request leave to amend its answer and counterclaims to assert invalidity based on inequitable conduct. Despite Mylan's tactical maneuvers, designed to hamstring Takeda's ability to confront this new theory, the Court granted Mylan's request. The Court explained that it was doing so because of the public interest in having issues decided on the merits, and not based on a finding either that Mylan had acted with sufficient diligence or that it had a good faith basis for its claim.

Mylan argues that the Court must have found "good cause" for Mylan's amendment of its pleadings to add the inequitable conduct claim since the Court applied that Rule 16, Fed.R.Civ.P., standard when granting the motion to amend. Mylan asserts that it was delayed in bringing its claim of inequitable conduct by Takeda's failure to complete document production until February 4, 2005, and Mylan's need to translate Japanese documents. It points out that its claim rested in large part on the assertion that back-up for test results listed in Takeda's internal reports and presented to the PTO could not be located in Takeda laboratory notebooks. *See* Opinion at 390. Mylan as-

serts that it notified the Court and Takeda through a letter of March 15, 2005, that Takeda may have procured its patent through inequitable conduct.

Mylan further contends that its assertion of inequitable conduct based on compound 3894 was not frivolous because Takeda did not advise the PTO that both pioglitazone and compound 3894 were both five times more potent than ciglitazone despite internal reports indicating that to be true. Further, it argues that since the data indicated that compound 3894's heart toxicity was "at the lowest level used by Takeda to indicate toxicity," the materiality of the omission of a discussion of the compound in the application for the patent was a "close question." Mylan points out that the Opinion containing the judgment of this Court following trial discussed these issues over the course of several pages, which must indicate that the issues were "worthy of serious consideration."

As the Court explained to the parties at the time, its decision to allow Mylan to bring its claim of inequitable conduct was absolutely not a finding that it was timely or meritorious. Nor can the February production of documents justify the assertion of the claim, since the claim was always frivolous. Mylan's assertions about compound 3894 were particularly egregious, and its continued defense of that assertion in this motion practice is inexcusable. Mylan's expert Hendry admitted at trial that compound 3894 was not the closest prior art to pioglitazone, and by the time of summations Mylan had abandoned any claim that it was. Opinion at 397 n. 104. At trial, Mylan scrambled to try to avoid the evidence that the compound was cardio-toxic by, for example, suggesting

that further testing and further statistical analysis of the test results were necessary to confirm the toxicity. Mylan did neither, however. Takeda did the additional statistical analysis and reconfirmed the reliability of the finding. *Id.* at 397-98 and nn. 103 & 104.

Mylan does not and cannot point to any passage in the Opinion of February 21, 2006 that suggests that any of its arguments were meritorious. While Takeda conceded that it had made two errors in describing the protocol for its testing to the PTO, neither of those errors was material, neither would have come close to supporting a finding of inequitable conduct, and Mylan does not suggest anything to the contrary in opposing this motion. The Opinion's length was driven in large part by the defendants' presentation of so many different arguments and iterations of those arguments. To place the findings of fact in context it was necessary to explain the history of the discovery of pioglitazone and the science relevant to the many issues raised by the defendants' claims. The length of neither that Opinion nor this can be fairly read as evidence that the defendants' claims had any merit. They did not.

Mylan contends that it had reason to question Fujita's credibility since Takeda was unable to produce laboratory notebooks to confirm all of the experimental data reported in Takeda's internal reports. As was noted above, Fujita led the research effort that resulted in the discovery of the pioglitazone molecule and was named as co-inventor on the '777 Patent. Fujita, who had been long retired from Takeda by the time of this litigation, did not undertake the search

for the notebooks during the discovery period and opined that the contemporaneous internal Takeda reports that he authored were reliable and that if notebooks could not be found for some of the results, then some of the notebooks must be missing. *See* Opinion at 390. There is absolutely no basis to argue, much less find, that Fujita was ever anything but honest.

Mylan asserts that Takeda's motive to mislead the PTO can be found in the admission by an Upjohn witness that patentability was something you are always concerned about, and Mylan's speculation that Takeda did not want to disclose compound 3894 to the PTO because it was well-known in the prior art and not patentable, and yet "comparable to pioglitazone in activity and toxicity." Mylan was not even aware of the existence of this Upjohn witness at the time it moved to amend and plead its inequitable conduct claim. In any event, the Upjohn witness testified at trial that patentability was not a driving consideration since Takeda and Upjohn were focused first and foremost on identifying a compound that was effective with extremely low toxicity. As just explained, Mylan's assertion that compound 3894 was comparable to pioglitazone is absolutely false and misleading. It could not establish that proposition at trial, and the repetition of the assertion in this motion practice further warrants the award of sanctions.

Takeda has shown that in each of the seven ways it has identified Mylan acted without a reasonable basis and in bad faith in pursuit of its inequitable conduct claim. For these reasons, Takeda is entitled to attorneys' fees for the period following the close of fact dis-

covery.

C. Mylan's Other Litigation Misconduct

Takeda also moves for sanctions because other misconduct by Mylan increased the expense and burden of the litigation. It asserts that Mylan (1) disobeyed court orders setting the schedule for depositions and requiring Mylan to produce a 30(b)(6) witness to respond fully to a deposition notice; (2) on the eve of trial tried to revisit earlier discovery rulings; (3) improperly tried to supplement its inequitable conduct theory on the eve of trial and prevent Takeda from responding to the attempt; (4) made an untimely motion for reconsideration regarding a ruling on a motion in limine concerning Hendry, then purported to withdraw it, only to reverse course again in an attempt to reassert the motion.

Mylan does not address the first issue. It asserts that Takeda suffered no prejudice from Mylan's eve of trial efforts, as set out in items 2 and 3, since the Court rebuffed them. As to the fourth item, it asserts that it fully withdrew the motion for reconsideration, and Takeda was never burdened with the necessity of responding to it in writing.

By themselves, these actions would not support a finding that this is an exceptional case that warrants an award of attorneys' fees. When taken together with the remainder of Mylan's misconduct, however, Takeda has shown that in each instance these actions constitute litigation misconduct and supply additional support for the award.

D. Mylan's Remaining Arguments in Opposition

None of Mylan's arguments in opposition to this motion are persuasive or alter the conclusion that the totality of Mylan's conduct in this litigation justifies an award of attorneys' fees. Mylan's opposition to this motion rests principally on policy arguments. It contends that Congress intended to foster ANDA patent litigation when it enacted the Hatch Waxman Act, that twenty-two of the thirty ANDA litigations that yielded a court decision have been decided in favor of the ANDA applicants, and that in nine of those cases the patent was ruled invalid.

There is no basis to find that this award of fees will deter ANDA filings and litigation. This award addresses baseless ANDA filings and the pursuit of frivolous ANDA litigation in bad faith and other litigation misconduct. The Hatch-Waxman Act cannot be read to immunize such conduct.

Mylan also requests a stay of a decision on this motion pending a ruling by the Federal Circuit on the appeal from the judgment entered at the conclusion of the trial and/or the completion of the litigation on the combination use patents. Mylan's previous request for a stay was denied, and will not be reconsidered here.

Mylan contends that a decision on the motion should not be made because the Court needs to weigh the amount of attorneys' fees being sought, and Takeda has not yet presented a request for a specific award. The amount of any award will be decided after Takeda has submitted its request for a specific amount

and the parties are given a full opportunity to be heard as to the size of any award.

Mylan asserts that Takeda's motion should be denied because Takeda (1) moved for an award of attorneys' fees against Mylan in its pre-trial memorandum of law dated November 18, 2005 on the ground that Mylan had filed a baseless Paragraph IV certification, when *Glaxo*, 376 F.3d at 1351, bars an award when the filing is the sole basis for the motion; and (2) served a bill of costs on April 11, 2006, although a notice of appeal had already been filed and costs cannot be taxed during the pendency of an appeal. As for Takeda's November 18 motion, it did not seek sanctions based on the filing of the certification, but on the grounds both that the certification was baseless and that Mylan had committed "myriad acts of litigation misconduct." Takeda did not catalogue the misconduct in its pretrial memorandum, but has done so now. As for the bill of costs, Takeda explains that it filed it within the time required by the local rule.

Mylan argues that no fees that Takeda incurred before June 6, 2005 should be awarded against it since that is the first date of misconduct alleged by Takeda against Mylan. June 6 is the date Mylan served its supplemental interrogatory responses and asserted for the first time that the '777 Patent was invalid for obviousness on the basis of the prior disclosure of compound 3894. Because Mylan had filed its certification in bad faith, and thereafter participated in the litigation over the validity of the '777 Patent on a frivolous claim of obviousness, it was in a position to move to amend its pleading and assert the claim of inequitable conduct. These actions were inextricably

intertwined, and the application to limit the award to the period following June 6, 2005 is denied.

Alphapharm and Mylan point to the remarks of the Court at the conclusion of the trial in which the Court thanked the parties for their hard work and level of preparation. The comments accurately reflect the hard work that each party put into the actual presentation of the evidence during trial, but said nothing about the merits of the parties' legal positions. Those positions were described in the Opinion and here. For the reasons set forth herein, Mylan's case is exceptional and an award of attorneys' fees against Mylan as well as Alphapharm is entirely justified.

Conclusion

Takeda's motions for an award of attorneys' fees is granted as to both Mylan and Alphapharm.

SO ORDERED.

S.D.N.Y.,2006.
Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.
459 F.Supp.2d 227

United States District Court,
S.D. New York.

TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,

v.

MYLAN LABORATORIES, INC., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc., Defendants.

Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc., Plaintiffs,

v.

Alphapharm Pty. Ltd. and Genpharm, Inc., Defendants.

Nos. 03 Civ.8253(DLC), 04 Civ.1966(DLC).

Feb. 21, 2006.

Background: Owner of patent for diabetes drug brought infringement actions against proposed manufacturers of generic versions. Manufacturer challenged validity of patent.

Holdings: The District Court, Cote, J., held that:
(1) patent was not invalid as obvious, and
(2) owner did not engage in inequitable conduct.

Judgment for owner.

Anthony J. Viola, Barbara L. Moore, David G. Conlin, Andre K. Cizmarik, Edwards Angell Palmer & Dodge, LLP, New York, NY, for Plaintiffs.

Martin B. Pavane, Edward V. Di Lello, Mindy H. Chettih, James P. Doyle, Cohen, Pontani, Lieberman & Pavane, New York, NY, for Defendants Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc.

Edgar H. Haug, Kevin F. Murphy, Jeffrey A. Hovden, Frommer Lawrence & Haug LLP, New York, NY, for Defendants Alphapharm Pty. Ltd. and Genpharm, Inc.

OPINION & ORDER

COTE, District Judge.

Takeda Pharmaceutical Company Limited ("Takeda") and Takeda Pharmaceuticals North America, Inc. ("Takeda North America") have brought this patent action under the Food Drug Cosmetic Act, 21 U.S.C. §§ 301-99, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub L. No. 98-417, 98 Stat. 1585 (1984) (codified in scattered sections of titles 21, 35, and 42 U.S.C.) (the "Hatch-Waxman Act"), and under the patent laws of the United States, alleging that four generic drug manufacturers have infringed and will induce infringement of Takeda's patents protecting its product ACTOS®, a drug used to treat Type 2 diabetes.

This Opinion presents the findings of fact and conclusions of law following a bench trial held between January 17 and January 30, 2006, to resolve the challenges made by defendants to Takeda's U.S. Patent No. 4,687,777 (" '777 Patent"), which protects the invention of the chemical compound 5-% 8B4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione ("pioglitazone"). Alphapharm Pty. Ltd. and Genpharm, Inc. ("Alphapharm") contend that the invention is obvious based on the disclosure by Takeda of a structurally similar molecule in the prior art. Mylan

Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. ("Mylan") contend that Takeda deceived the Patent and Trademark Office ("PTO") when it applied for the '777 Patent, principally by misrepresenting the results of efficacy and toxicity tests. Neither challenge is meritorious. The length of this Opinion is occasioned by the need to address the many iterations of the defendants' arguments, as they searched for a viable theory to attack the '777 Patent.

As described below, the '777 Patent discloses a remarkable invention. After decades of work to develop an anti-diabetic treatment, Takeda discovered a pharmaceutical agent that was both effective and non-toxic. This represented a significant advance over compounds disclosed in the prior art. Takeda's application to the PTO for the '777 Patent reported the very analysis of test results on which Takeda itself had previously relied to select the pioglitazone molecule from the thousands it had synthesized and the hundreds it had tested. Faced with the task of proving their cases by clear and convincing evidence, both Alphapharm and Mylan have failed to make even a rudimentary showing that the invention was obvious or that Takeda engaged in inequitable conduct. Their challenges to the '777 Patent are rejected.

Trial Procedure

The trial was conducted in accordance with the Court's Individual Practices and the Scheduling Order dated July 20, 2004. The parties filed a Joint Pretrial Order and accompanying memoranda of law and proposed findings of fact and conclusions of law on

November 18, 2005. The parties also served affidavits containing the direct testimony of all their witnesses, as well as copies of all the exhibits and deposition testimony which they intended to offer as evidence in chief at trial.

A science tutorial was held on December 1, 2005. Testifying for Takeda were Silvio Inzucchi ("Inzucchi"), a Professor of Medicine at Yale University and expert endocrinologist who serves as the Director of the Yale Diabetes Center; James Hendrickson ("Hendrickson"), the Henry F. Fischbach Professor of Chemistry, retired, at Brandeis University and an expert in organic chemistry; and Peter Valberg, a senior scientist at a private environmental health consulting firm, an expert in the statistical analysis of animal testing data, and formerly an Associate Professor of Physiology at Harvard's School of Public Health. Testifying for Alphapharm was Henry Mosberg ("Mosberg"), a Professor of Medicinal Chemistry at the University of Michigan, and an expert in drug design. Testifying for Mylan was Lawrence Hendry ("Hendry"), an Adjunct Professor of Physiology and Endocrinology at the Medical College of Georgia, an Associate Adjunct Professor of Medicinal Chemistry at the University of Georgia, and the founder of a chemical design firm.

The plaintiffs and defendants were each given twenty-four hours for opening statements, examination of witnesses and evidentiary arguments at trial. Of the time granted the defendants, Alphapharm was given eight hours and Mylan sixteen hours.[1] The parties were given additional time for summations.

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[1] When the defendants exhausted their time at trial, they were given a limited amount of additional time.

In addition to the experts who testified on December 1, the following witnesses testified at trial. For Takeda, Richard Daly, Senior Vice President of Marketing at Takeda North America; William Kettyle ("Kettyle"), an expert endocrinologist with significant expertise in the treatment of diabetes; Loren Koller ("Koller"), a doctor in veterinary medicine, an environmental health and toxicology consultant, an expert in immunotoxicology, and an officer of the Association for Assessment and Accreditation of Laboratory Animal Care International; Takeshi Fujita ("Fujita"), a former Takeda employee who, as the Chief Scientist of Takeda's Biology Research Laboratory, was the co-inventor on the '777 Patent; Samuel Danishefsky ("Danishefsky"), a Professor of Chemistry at Columbia University who holds the Kettering Chair at the Memorial Sloan-Kettering Cancer Institute; Yasuo Sugiyama, Takeda's Manager of Strategic Research Planning and a researcher who was involved in the development of pioglitazone; Bernard Landau ("Landau"), a Professor of Biochemistry at Case and Western Reserve University, and, in 1996, a Nobel Fellow at the Karolinska Institute in Sweden; Bruce Stoner ("Stoner"), a former Chief Administrative Patent Judge; Gerard Colca ("Colca"), a former senior research scientist in metabolic disease research at The Upjohn Company ("Upjohn"), a U.S. pharmaceutical company that had worked with Takeda in the development of pioglitazone; and Douglas Morton, a former Director of Diabetes and Gastrointestinal Diseases Research at Upjohn.

Testifying for Alphapharm was Richard Wright, a Professor of Economics at the University of California

at Berkeley, and a member of the Steering Committee for Berkeley's Center for Hunger and Obesity. Testifying for Mylan was Martin Ronis ("Ronis"), a Professor of Medicinal Sciences at the University of Arkansas, Associate Director of the Arkansas Childrens' Nutrition Center and an expert in chemical testing in animals. Mylan also presented the declaration of Mark Nusbaum ("Nusbaum"), a former Examiner-in-Chief and member of the Board of Patent Appeal and Interferences.[2]

The parties also offered excerpts from the deposition testimony of some of the fact witnesses that testified at trial and of the following individuals: Michael Davis, the American patent attorney who prosecuted the '777 Patent; Yoshikazu Hasagawa, the Senior Manager in charge of Intellectual Property litigation for Takeda; Shelly Monteleone, Intellectual Property Counsel for Mylan; Brett Mooney, an Alphapharm employee involved in pharmaceutical development; Hiroyuki Odaka, a former Takeda employee who worked in Takeda's Biology Research Laboratories at the time of the development of pioglitazone; Brian Roman, an attorney and a Rule 30(b)(6) witness for Mylan; Howard Rosenberg ("Rosenberg"), the Group Intellectual Property and API Strategy Director for Generics U.K., a sister company of Alphapharm, and an Alphapharm Rule 30(b)(6) witness; Michael Rosenberg, the owner of Health Decisions, a company engaged in clinical research; Takashi Sohda, General Manager of Takeda's Pharmaceutical Research Division; Barry Spencer, a Senior Patent Officer at Alphapharm and a Rule 30(b)(6) witness for Al-

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[2] Takeda chose not to cross-examine Nusbaum and thus he did not appear at trial.

phapharm; Shigehisa Taketomi, a Takeda employee and Rule 30(b)(6) witness for Takeda; and Stephen Talton, a Mylan employee responsible for preparing applications to sell generic drugs.

The findings of fact based on the evidence presented at trial are scattered throughout this Opinion. The background section contains the story of the development of pioglitazone, an introduction to the prior art, a description of the relevant patents and their file histories, an introduction to the science that is necessary to understand the discussion that follows, and an outline of the procedural history of this litigation. The discussion section of the Opinion will address first the issue of obviousness and then the issue of inequitable conduct.

Background

A. Diabetes

Diabetes is a disease in which the body is unable to metabolize blood sugar or glucose derived from food, primarily carbohydrates, into energy efficiently. The blood glucose level is essentially controlled by insulin, which drives the process whereby glucose enters the cells of the body and is turned into energy. Insulin is a hormone made by specialized cells within the pancreas called beta cells.

There are two types of diabetes. Type 1 diabetes is characterized by the fact that the pancreas does not produce insulin. Insulin must therefore be supplied from an external source, such as an injection or insulin pump. Type 1 diabetes compromises less than 10%

of diabetes cases worldwide.

In Type 2 diabetes, the body fails to utilize effectively the insulin that is produced. This failure usually starts in the muscles, which collectively use most of the glucose produced by the body. The liver is also responsive to insulin, which instructs the liver when to stop making glucose. When the liver becomes insulin resistant, it resists those instructions and continues to create glucose. Insulin resistance also impacts the pancreas, at first by forcing it to produce more insulin than normal. Over time, the increased resistance to the action of insulin overwhelms the ability of the pancreas to produce sufficient insulin, and the symptoms of diabetes begin to appear. If Type 2 diabetes is left untreated, the demand for insulin from the pancreas can eventually lead the beta cells to become dysfunctional, a phenomenon known as "exhaustion" or "burn-out."

Diabetes can cause great damage to the body. Due to the toxic effects of high glucose on blood vessels, patients with diabetes are predisposed to chronic complications such as kidney failure, blindness, leg ulcers and amputations, heart attacks, and strokes.

B. Treatments of Diabetes

Type 2 diabetes may be treated with lifestyle changes, such as weight loss, improved diet, and exercise. These steps are rarely sufficient. A substantial portion of patients ultimately need injections of insulin. Insulin is effective because insulin resistance in Type 2 patients is not complete-insulin may still lower blood glucose.

The past twenty-five years have seen the development of a number of oral antidiabetic drugs ("OAD") that are used instead of, or in conjunction with, insulin. Different classes of OADs have that have been developed work in the different parts of the body affected by diabetes. It is common practice to treat diabetes with a combination of several classes of drugs.

Sulphonylureas, which became available in the 1980s, are the oldest class of drug used to treat Type 2 diabetes, and work by stimulating the pancreas to secrete more insulin. Meglitinides work very much like the sulphonylureas but differ in that their onset is more rapid and their duration of action is briefer.[3] Biguanides help to reduce the liver's production of glucose. Metformin®, a biguanide, is frequently the first drug chosen to treat a newly diagnosed Type 2 diabetes patient. It became available in 1995.

The treatment of diabetes was revolutionized in the 1990's with the introduction of a class of drugs known as thiazolidinediones ("TZDs"). TZDs were first discovered by Takeda in the 1970s. They are peripheral insulin sensitizers, working within muscles to enhance the effect of insulin in that organ, and thereby to increase the muscles' ability to take glucose from the bloodstream.

The first TZD to be marketed in the United States was troglitazone, known by the commercial name

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[3] Alpha-glucosidase inhibitors, which are used infrequently in the United States, interfere with starch absorption in the intestine, thereby slowing the increase in blood glucose levels after meals.

Rezulin®. Rezulin®, which was developed by Pfizer, first became available in 1997. In May of 1999, two years after Rezulin® entered on the market, the Food and Drug Administration ("FDA") approved GlaxoSmithKline's Avandia® (whose active ingredient is rosiglitazone). The drug at issue here, ACTOS®, which was approved by the FDA in July of 1999, is the only other TZD currently approved by the FDA for sale in the United States.

In March 2000, Pfizer withdrew Rezulin® from the United States market due to significant concerns about its safety. After Rezulin® was withdrawn, ACTOS® and Avandia® essentially split the TZD market in the United States. More recently, research has shown that these two TZDs have a greater positive effect in the treatment of cardiovascular disease than other anti-diabetic drugs, and that ACTOS® in particular has a greater impact than Avandia® on lowering cardiovascular risk.[4] Based in part on this research, there is evidence that ACTOS® is becoming the preferred TZD among knowledgeable doctors.

By any measure, ACTOS® has been a hugely successful commercial product. It has led the TZD market for new prescriptions written by endocrinologists since February 25, 2000. In October 2001, it became the seventh fastest product in pharmaceutical history to reach $1 billion in annual sales.

C. Takeda's Research into Diabetes

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[4] To reduce cardiovascular risk both trigylcerides and LDL-cholesterol should be lowered. Pioglitazone has shown better trigylceride lowering properties than rosiglitazone and also has shown less of an effect of raising LDL-cholesterol.

Takeda, a Japanese pharmaceutical company, is based in Osaka, Japan. Takeda North America is a wholly owned United States subsidiary of Takeda America Holdings, Inc., which is a wholly owned subsidiary of Takeda.

Takeda began its research into obesity and related diseases in the early 1960s. Working with Nagoya University in Japan, Takeda developed an animal model that exhibits the symptoms of diabetes: KKA^{y} mice. This is an obese strain of mice that consistently exhibits symptoms of insulin resistance under normal diet conditions. Takeda researchers also developed the genetically obese and diabetic Wistar fatty rat. The development of the KKA^{y} mouse and the Wistar fatty rat were significant steps in the effort to develop pharmaceutical treatments for diabetes since compounds could now be tested in diabetic animals.

Takeda made a pharmacological breakthrough in the 1970s. Takeda researchers discovered the first TZD derivative compound and learned that TZDs exhibited considerable blood glucose lowering effects in KKA^{y} mice.[5] The defining characteristic of TZDs is the presence of a thiazolidinedione group at the right end or moiety[6]of a molecule.

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[5] Takeda's diabetes research was conducted through a partnership of Dr. Yutaka Kawamatsu, who ran the chemical research into TZDs and Fujita, who oversaw the biological research.

[6] A moiety is a "group of atoms forming a distinct part of a large molecule." Oxford English Dictionary (Draft Revision to 2d Ed. December 2003). Tabular or graphic material set at this point is not displayable.

Takeda's work with TZD derivatives revealed that at least some compounds within the TZD class did not lower blood glucose in normal, non-diabetic animals. This was another important finding because it suggested that TZD derivatives did not affect the level of insulin in the body, but instead were insulin sensitizers, a term for compounds that ameliorate insulin resistance, the defining characteristic of Type 2 diabetes.

While scientists did not initially understand how TZDs work, and still debate today precisely how TZDs actually function within the body, there is a growing consensus that TZDs enhance the signal of insulin receptors that reside in the cells that require or store energy, such as muscles and fat cells. When we eat, the level of glucose rises in the bloodstream, stimulating the pancreas to secrete more insulin. The insulin which is flowing through the blood binds to insulin receptors, causing changes inside cells that allow glucose to enter the cell from the bloodstream, where it can be burned for energy or stored. Because of a negative feedback system, as the level of glucose in the blood falls, the pancreas produces less insulin so that the blood glucose returns to normal levels.

TZDs activate the insulin receptors by binding to a molecule within the cell's nucleus known as PPAR-gamma. Together, they bind to specific areas on the cell's DNA, producing messenger RNA and effectively stimulating the production of glucose transporters within the cell. The transporters travel to the surface of the cell and facilitate the entry of glucose into the cell from the bloodstream.

Scientists still do not fully understand how insulin resistance works at the cellular level, but it is believed that the problem relates to the interaction between the insulin receptors and that section of the DNA in the cell's nucleus that is responsible for triggering the production of glucose transporters. As noted, TZDs work by binding with a molecule in the nucleus of the cell called PPAR-gamma. When that happens, the PPAR-gamma molecule changes shape and binds to the DNA in the cell. Each TZD seems to bind differently with the PPAR-gamma. As a result, different TZDs have different metabolic effects. TZDs also bind with other PPAR molecules in the cell, such as the PPAR-alpha and PPAR-delta molecules, further contributing to the differences among TZDs.

The fact that TZDs affect the gene transcription process within DNA makes them both effective but also unpredictable. Only a fraction of the genes in the human body have been identified. It is possible that TZDs stimulate genes that are still unknown. As one of Takeda's expert endocrinologists has explained, gene transcription is "a big black box.... When you are stimulating a gene, you can do a lot of things downstream that you may not understand."

D. The Development of Ciglitazone and the '200 Patent

Takeda's research led to the synthesis of the TZD ciglitazone in February of 1978. Takeda worked for many years to develop ciglitazone, only abandoning it when it proved toxic during human clinical trials. Thereafter, Takeda's search for a TZD to develop as a commercial pharmaceutical used ciglitazone as a

benchmark. Takeda searched for a compound that was more potent than ciglitazone, which required unrealistically high doses to be effective, and yet nontoxic.

Ciglitazone's chemical structure is illustrated here:

Tabular or graphic material set at this point is not displayable.

It was identified as a particularly promising compound based on its blood glucose lowering effect in KKA^y mice. Based on this research, Takeda filed a United States patent application on July 27, 1979, covering a generic class of TZD derivatives including ciglitazone. The application eventually resulted in the issuance of U.S. Patent No. 4,287,200 (" '200 Patent").

The application for the '200 Patent (" '200 Application") made eight claims. Its first claim was its broadest and covered hundreds of millions of TZD compounds through a formula that allowed for a wide variety of chemical structures on the left-hand end to be attached to the TZD structure on the right. The '200 Application represented that TZDs are "novel compounds and useful as, for example, remedies for diabetes, hyperlipemia and so on of mammals including human beings."

The '200 Application was the subject of two office actions by the PTO. The second office action allowed two of the eight claims, but rejected all of the other claims as containing "improper Markush groups." *See Ex parte Markush*, 1925 CD 126, 340 Off. Gaz. Pat.

Office 839 (Comm'r.Pat.1925).[7] The office action identified three separate groups the patent examiner believed were contained in the '200 Application.[8]

In response to the second office action, Takeda amended its application to cover only the first of the three groups identified by the examiner. In the amendment Takeda noted that it might file "divisional applications" to cover the other groups.

The '200 Patent was issued on September 1, 1981. Fujita and Dr. Yutaka Kawamatsu were named as coinventors. In addition to the generic class of TZDs, the patent also presented, as examples, sixty specific compounds covered by the generic formula. Included among those disclosed was compound 42, whose left end was a 2-pyridyl ring with a methyl at the 6-position. Compound 42 is a compound of importance to this litigation and is discussed in detail below.[9] Like ciglitazone, compound 42 had first been synthesized in 1978.

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[7] The examiner cited a recent appellate decision, *In re Harnisch*, 631 F.2d 716 (C.C.P.A.1980), as providing a legal basis for the rejection. *Harnisch* confirmed the concept of an "improper Markush group" as a basis for rejecting a patent application. *Id.* at 721. The decision explained that the issue underlying improper "Markush groups" was better described as a lack of "unity of invention." *Id.*

[8] The three groups identified were distinguished by the possible structures on the left end moiety. Group A was composed of compounds where the left end moiety contained an alkyl, cycloalkyl or phenylalkyl; for Group B the left end contained a thienyl or furyl; for Group C the left end contained a pyridyl or thiazolyl. It is this last group that is of importance here; pioglitazone is a left end pyridyl.

[9] Compound 42 from the '200 Patent is compound (b) from the '777 Patent.

E. Two Divisional Patents

Takeda obtained two divisional patents for the '200 Patent. First, through a patent issued on July 20, 1982, as U.S. Patent No. 4,340,605 (" '605 Patent"), Takeda received a patent for the third group identified by the examiner.[10] In support of the application for that patent, Takeda presented a declaration from Fujita providing data for blood glucose and lipid lowering effects of twelve compounds tested in KKA^{Y} Mice, including compound 42 from the '200 Application.

On July 7, 1982, Takeda filed an application for a second divisional to the '200 Patent. The patent, which issued on March 20, 1984, as U.S. Patent 4,438,141 (" '141 Patent"), covered the second grouping that was identified by the examiner in the course of prosecuting the '200 Patent.

F. Sohda II

While it was securing the '200 Patent, Takeda continued its research into TZD derivatives and by early 1982 had evaluated approximately 1000 compounds for their potential as antidiabetic agents. Important information about TZDs and Takeda's research efforts was published in a series of articles by Takeda's scientists. Of particular importance to this Opinion, because it constitutes prior art for the '777 Patent,

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[10] The third group identified, compounds with a pyridyl or thiazoyl on the left end, had been designated group C by the examiner.

was an article received for publication on April 22, 1982, T. Sohda et al., *Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy-benzyl]) thiazolidine-2,4-dione (ADD-3878) and its Derivatives,* Chem. Pharm. Bull., 30:3580-3600 (1982) ("Sohda II"). Sohda II did not disclose pioglitazone, but it did disclose a compound that was structurally close to pioglitazone, and which Alphapharm contends made the invention of pioglitazone obvious.

Sohda II described 101 specific TZD compounds, giving data on each compound's efficacy. As was the case in the Fujita declaration submitted in the prosecution of the '305 Patent, the data were presented as a score ranging from one to four in two categories: hypoglycemic activity (blood sugar lowering activity) and plasma triglyceride lowering activity. A higher score represented greater potency.

While the article did not present data on the toxicity or side effects of the compounds, it did comment on these issues for particular compounds. Of the 101 compounds, the article identified three compounds-compounds 47, 49 and 59-as showing the most favorable profiles "in terms of activity and toxicity." The article concluded that those three compounds "may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity." Compound 49 was ciglitazone and compound 47 was a compound whose left end was structurally similar to ciglitazone's. The left end of compound 59 was different from 47 and 49, its left end terminated with a 3-pyridyl ring.

Since pioglitazone has a pyridyl ring at its left end, it

is important to discuss compound 59 and related compounds described in Sohda II in some detail. To begin with, the term pyridine refers to a six-membered carbon-containing ring with one carbon replaced by a nitrogen. A pyridyl ring is diagramed as follows:

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The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion. As noted, compound 59 was a 3-pyridyl ring, which means that the ring is attached at the third position to the rest of the molecule.

The article disclosed two 2-pyridyl compounds: compound 57, the unsubstituted 2-pyridyl, and compound 58, the 6-methyl substituted 2-pyridyl. The term unsubstituted indicates that the pyridyl ring does not have any substituents (such as a methyl or ethyl group) linked to it, while the term 6-methyl indicates that a methyl is linked to the ring at the 6 position, using the numbering system described above. Diagrams of the two compounds are presented below:

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Compound 57 from Sohda II was designated by Takeda as Compound 3894 ("Compound 3894"), and compound 58 was designated Compound 3959 ("Compound 3959") and identified in the '777 Patent as compound (b). The defendants' challenges to the '777

Patent largely hinge on assertions concerning these two compounds, and they will generally be referred to as compounds 3894 and (b) in the course of this Opinion.[11]

The 101 compounds described by Sohda II were organized into seven groups. The article commented on characteristics associated with compounds in each of the seven groups. When discussing the group into which compounds 57 and 58 fell, it noted that "[a]lthough compounds 56, 57, 58, 59 and 63 ... showed potent activities, they, *especially 57 and 58,* caused considerable increases in body weight and brown fat weight," in the rodents in which they were tested. (Emphasis supplied.)

In the 1980's, scientists believed, as they do today, that increases in body weight are not desirable for diabetics. There was disagreement, however, about the implications of an increase in brown fat in rodents for humans treated with the same compound. Adult humans have relatively little brown (as opposed to white) fat, while rodents carry a significant amount of brown fat in the saddle between their scapulas. Brown fat has a thermogenetic effect, generating heat to keep them warm. At the time that Sohda II was written, overall weight and fat gain caused by pharmaceuticals were thought to correlate in mammals, including rodents and humans.

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[11] As already noted, compound (b) had previously been disclosed by Takeda as compound 42 in the '200 Patent, and was also one of the twelve compounds later listed in the Fujita declaration that accompanied an amendment to the application for the '605 Patent.

G. The Third Divisional Patent: The '779 Patent

On March 15, 1983, Takeda filed a third divisional patent to the '200 Patent. The application sought to expand the grouping of compounds originally covered by the '605 Patent, by adding compounds where "the pyridyl or thiazolyl groups may be substituted."[12] FN12 A preliminary amendment also noted that compounds in which "hetrocyclic rings are substituted have become particularly important, especially Compound 42 in example 9." Compound 42 was the compound destined to be used as a comparator in the '777 Patent, where it is listed as compound (b).

Because the application only sought to expand the groups covered by the '605 Patent but not to introduce a substantively different claim, Takeda filed a terminal disclaimer, noting that the "inventive entity" covered by the '605 Patent and the application were the same, and thereby disclaiming any protection of the compounds in this application beyond the expiration of the '605 Patent. The application was approved by the PTO and issued on April 24, 1984, as U.S. Patent No. 4,444,779 (" '779 Patent").

H. The '902 Patent

Takeda's patent prosecutions were not limited to the divisionals of the '200 Patent. On December 29, 1982, Takeda filed an application covering TZD derivatives with a cyclohexane ring on the left end.[13] The patent

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[12] A thiazolyl is a five member heterocycle, with a nitrogen and sulfur at positions 1 and 3, respectively.

[13] A cyclohexane ring is a saturated ring of six carbons. Ciglitazone's left moiety contains a cyclohexane ring.

issued on July 24, 1984 as U.S. Patent 4,461,902 (" '902 Patent").

I. The Failure of Ciglitazone

After Takeda's TZD development program attracted the interest of Upjohn, Takeda and Upjohn worked together on the development of ciglitazone from 1981 to 1983. Both companies analyzed the compound's anti-diabetic properties and toxicity, and based on those studies, began Phase I safety studies with human volunteers in both the U.S. and Japan.

As work on the development of ciglitazone progressed it became evident that the compound could not be successful as a commercial anti-diabetic. In November 1982, it was determined that ciglitazone caused cataracts in rats that were being treated with the compound as part of a ninety-day toxicology study. Upjohn believed that the FDA would block a compound that caused cataracts from the U.S. market. Second, a clinical trial in Japan suggested that ciglitazone might not be effective for a Type 2 diabetic patient unless the dose was above 500 milligrams per day, a dosage which was impractical. By 1983, Takeda and Upjohn renewed their search for a more potent, non-toxic compound.

J. Initial Development of Pioglitazone

Meanwhile, Fujita was working with Dr. Kanji Meguro ("Meguro"), the Chief Scientist of the Chemical Research Laboratory at Takeda, to develop ideas for new compounds to be synthesized and tested. On September 7, 1982, pioglitazone was synthesized. It

terminates at its left end in a 2-pyridyl ring with an ethyl at the 5 position on that ring.[14] It was given the internal Takeda compound number 4833.

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The first screening of pioglitazone for efficacy in November 1982 noted its promise:

Initial Screening

> 10 Samples were tested in KKA^{y} mice. 2 samples were significant in lowering blood glucose. The effect of AD-4833 was relatively strong, 0.005% food admixture 4-day administration resulted in reducing blood glucose, plasma TG and NEFA by 46%, 31% and 30% respectively. No significant increase in body weight was observed. The effect was weaker than that of ADD-3959 [identified as compound (b) in the '777 Patent].[15]

Takeda scientists also conducted preliminary toxicity tests on compounds that showed promise. Pioglitazone was the least toxic of all the TZD compounds evaluated in 1983 and 1984.

Following the failure of ciglitazone, Upjohn and Ta-

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[14] An ethyl group is C2H5.Ethyl groups differs from methyl groups, CH3, by a single CH2 group. Ethyl and methyl are both lower alkyls.

[15] Takeda seems to have used both AD- and ADD- as prefixes when designating compounds during their research. No explanation has been given for any difference between the two prefixes. This Opinion does not use either designation.

keda renewed their collaborative research. In their search for a new compound they focused on the 130 TZD derivatives that had been tested during the ciglitazone selection process, but also synthesized some new compounds.

The decision by Takeda and Upjohn to continue to research TZD derivatives went against some of the thinking in the industry. Other leaders in the diabetes field believed that better avenues for research included developing insulin secretagogues (compounds which combat insulin resistance by causing the pancreas to create more insulin) and treatments for late-stage consequences of Type 2 diabetes, such as neuropathy, nephropathy, and retinopathy.

One of the compounds that was retested during this period was compound (b). Compound (b) had shown strong blood glucose lowering activity in mice and triglyceride lowering activity in both mice and rats. Despite its efficacy, compound (b) was dropped from consideration when testing revealed significant toxicity to the liver and heart as well as a decrease in the number of erythrocytes, a sign of potential toxicity to bone marrow. Compound (b) also failed the cataract screening test conducted by Upjohn.

Based on the experiences with ciglitazone and compound (b), Takeda made identifying a compound without toxic effects its highest priority. It was Upjohn's view that any compound that failed the in vitro chick lens assay test for cataractogenesis had to be ruled out from consideration for development.

K. Takeda's Testing Methods

Takeda conducted many efficacy tests on numerous compounds, including pioglitazone, throughout 1983 and 1984. In order to screen for efficacy, KKA^{y} mice or rats were treated with different dosage levels of a compound for four days. Initial tests usually involved just two doses of the compound to determine roughly if the compound was active. The dosage levels were calculated as milligrams of compound per kilogram of body weight of the treated animal per day (mg/kg/day). The researchers typically matched the animals to be tested by age, sex and body weight. From the pools of animals, groups of five animals were randomly chosen for each dosage level in the test and a separate group of five was chosen to serve as a control. On the fifth day of the screening, the blood glucose and triglyceride levels of the test animals were measured and were compared to blood taken from untreated control animals.

For many compounds Takeda also conducted three dose efficacy tests, to assist researchers in determining the dosage of a compound necessary to reduce an animal's blood glucose level or triglyceride level by 25%. The effective dose required to reduce the levels by 25% is called the "ED^{25}".

Takeda's experiments were performed by technicians. At the end of a three dose efficacy test, the technician would perform regression calculations to plot the best straight line between the three data points. The results would then be reviewed by a trained scientist or by Fujita in order to determine whether the points plotted or the line determined by the regression equation actually corresponded as well as it should to a

true dose response curve.

The relationships between two variables in biological systems, such as the changes in blood glucose concentrations with a change in a dosage of a drug, are usually not linear but rather exponential. Plotting the change of the one variable against the other will often result in a curve which is made linear through the application of a process called linear regression. There are limitations, however, on the reliability of a linear regression. A linear regression is more reliable if the interval between the data points is limited. It is significantly less reliable when the administered dosages do not fall within the effective dosage range of the compound being tested since including even one data point that is outside of the linear response region can significantly change the relationship between the three points plotted in a three-dose test. Extending a line beyond a data point to reach an ED^{25} value that was not within the tested range also runs a considerable risk that the projected results will be unreliable.

Takeda was testing new compounds whose properties were unknown and it had to guess what the best dosage range for testing might be. Not infrequently, it chose dosages that were above or below the effective dosage range. This meant that Takeda often had to conduct several experiments to improve its understanding of the effective dosage range of a compound. In addition to the challenges of making an accurate determination of the ED^{25} values, Takeda scientists also had to monitor the experiments for other possible factors that might make a particular experiment's results unreliable.

L. Report A-15-13

On February 8, 1984, Takeda forwarded a copy of Fujita's report A-15-13 ("Report A-15-13") to Upjohn. The report, which was titled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats", disclosed the results of preliminary toxicity studies conducted on fourteen compounds that Takeda had considered as candidates for development. The report detailed the method of testing that had been employed: oral doses of 100mg/kg/day of the test compound for two weeks given to five to six week old male and female Wistar rats. At the end of the testing period the rats were sacrificed, body weights and organ weights were analyzed, as were blood chemistry and hematology. The report contained the organ weight expressed as normalized weight (calculated by dividing the organ's weight by the weight of the rat and expressing the weight as a percentage) in order to compensate for the fact that animals differ in size. Pioglitazone was one of the compounds presented in Report A-15-13 and showed no statistically significant toxicity.

In addition to pioglitazone, several other compounds of interest to this Opinion were among the fourteen, including the unsubstituted 2-pyridyl (compound 3894) and the 5-methyl 2-pyridyl (compound (c) as designated in the '777 Patent). The introduction to the report noted that each of these three compounds was less toxic "in regard to reduction of blood red (sic) cells and hypertrophy of liver and heart which were common toxic effects in ciglitazone-related compounds." It added, "[c]onsidering the fact" that com-

pound 3894, pioglitazone and compound (c) "are five times as potent as ciglitazone in the pharmacological activities, they appear to be much easier to continue further studies including clinical trials." In point of fact, however, the report found that compound 3894 produced a statistically significant negative effect on the heart of male rats and that compound (c) had such an impact on platelets. Two other compounds that were used as comparators in the '777 Patent also demonstrated toxicity. Compound (b) was toxic to the liver, heart and erythrocytes, among others things, while compound (d) was toxic to the liver and heart.

M. March 1984 Plan

After two days of meetings between Takeda and Upjohn in March 1984, at Upjohn's headquarters in Kalamazoo, Michigan, the participants agreed that Takeda would select fifty TZD compounds based on hypoglycemic activity in both the KKA^{y} mouse and the Wistar-fatty rat. Upjohn was to test the leads identified by Takeda in the in vitro chick lens assay for cataractogenic activity, and Takeda was responsible for other toxicity testing.[16] Takeda had already provided Upjohn with KKA^{y} mice so that Upjohn could replicate Takeda's efficacy testing. It also gave Upjohn the fifty compounds that it had synthesized and selected for this intensive review.

The minutes of the March meeting reflect that it was "desirable that leads selected for further development are clean" in the chick lens assay. Based on a combination of the chick lens assay and the toxicity studies,

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[16] Takeda was to carrying out two-week toxicity studies for the leads in Wistar rats at 100 mg/kg/day.

nine to ten leads were expected to emerge and be subject to further testing by Takeda and Upjohn. It was anticipated that four to five leads would emerge from that further testing and proceed to ninety-day toxicity studies in both rats and dogs. Compounds which emerged as "clean" through all of the stages of testing would be "considered for further development with a goal of IND filing for the best compound as a drug candidate."[17] The minutes established a time line for each stage in the process. The next meeting, for selection of the nine to ten leads was scheduled for August 1984.

In selecting the fifty compounds, Takeda was also to consider the "uniqueness of chemical structure." The emphasis on the uniqueness of the chemical structure as a criterion for selecting the initial fifty compounds arose from a Takeda policy that candidate compounds should be reasonably unique from each other in their chemical structures because toxicological problems and adverse reactions are often caused by discrete chemical structures. By emphasizing variety in the chemical structures to be studied, Takeda hoped to avoid losing entire ranges of candidates due to a particular structure's toxicity.[18] Based on those same

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[17] An Investigational New Drug Application ("IND") is an application filed with the FDA to conduct clinical trials (i.e. tests on humans). *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, ----, 125 S.Ct. 2372, 2377, 162 L.Ed.2d 160 (2005).

[18] While Mylan argued that Takeda and Upjohn were concerned in 1984 not with identifying the best anti-diabetic treatment but with the patentability of a compound, the Takeda and Upjohn witnesses presented entirely credible testimony that they were driven by concerns about efficacy and safety. After all, a patent on a useless compound is useless.

concerns, Upjohn researchers endorsed the decision to make chemical uniqueness a selection criterion.

The fifty compounds chosen by Takeda were a mix of those that had already been tested in earlier research and those that Takeda had recently synthesized. Among the recently synthesized compounds were three that appeared as comparators in the '777 Patent: compounds (c), (d), and (e), which were first synthesized on July 21, May 4, and August 4, 1983, respectively. Because Takeda had observed that pioglitazone was comparatively potent and exhibited no toxicity it synthesized compounds that were structurally related so that it could compare the results.

Takeda's benchmark for efficacy was the ED^{25} of ciglitazone. The candidate compounds were continually evaluated from July through October of 1984 in order to find what Takeda scientists considered the most reliable ED^{25} values.

N. October 30, 1984 Meeting and Report A-15-34

Obtaining the efficacy and toxicity data for the candidate compounds turned out to be much more complicated and time consuming than expected. The meeting with Upjohn originally planned for August 1984 did not take place until the end of October. At the meeting Takeda presented Fujita's report A-15-34, which was titled "Pharmacological and Toxicological Studies of Ciglitazone and its Analogues" ("Report A-15-34"). This report is of critical importance to the issues of inequitable conduct raised by defendant Mylan.

Report A-15-34 lists fifty compounds in Table 1. The report gives the chemical structure of each compound as well as efficacy and toxicity data. In generating the report, Fujita examined all of the test results to locate the most reliable ED^{25} numbers for each compound. In addition to listing the ED^{25} score which he considered to be the most reliable for each compound, Fujita also indicated in a parenthetical the relative efficacy of each compound to that of ciglitazone. For instance, the benchmark for all testing, ciglitazone, was listed first with an ED^{25} for glucose lowering in KKA^y mice of "40 (1)".Pioglitazone was listed about one-third of the way down the table with an ED^{25} of "6 (6.7)", indicating that a dose of 6 mg (per kg per day) of pioglitazone achieved an ED^{25}, rendering it about 6.7 times more potent than ciglitazone, which required a dose of 40 mg to achieve that result. The parenthetical sometimes indicated the range of the test results obtained by Takeda.

Table 1 also indicated the results of the in vitro chick lens assays conducted by Upjohn. A compound failed the chick lens assay if it caused a change in pH or a cloudy appearance at a lower concentration than did ciglitazone.

Finally, the report provided summary data for hepatomegaly (liver toxicity), cardiomegaly (heart toxicity) and anemia (erythrocyte depletion) from two-week toxicology studies in male and female Wistar rats. The data were presented using a rating system based on the degree of toxicity. For liver and heart, toxicity was evaluated by a percentage gain in weight; for anemia, toxicity was evaluated by a percentage decrease of erythrocytes. Rather than give precise toxic-

ity numbers, the report listed three ranges of toxicity in terms of growth or decline: 8-20%, 21-25%, and 26% and above.

Fujita selected twelve of the fifty compounds as compounds on which the meeting participants should particularly focus their attention, and presented the data for these twelve on Table 2 in the report. In selecting the twelve, Fujita considered the potency of a compound in comparison to its performance in toxicity testing, including the chick lens assay tests, as well as the structural diversity of the compounds. Fujita selected only two compounds whose left end was a pyridyl ring. One of those two was pioglitazone. Pioglitazone was the only compound among the twelve that showed no toxicity, although many of the others listed on Table 2 were far more potent. None of the comparator compounds from the '777 Patent appear on Table 2, although all of them appear on Table 1 of Report A-15-34.

During the meeting, the scientists from Takeda and Upjohn reviewed the data for all the compounds presented in Table 1, giving particular attention to the twelve compounds on Table 2. The discussion was an open one and Upjohn was free to suggest that any compound from Table 1 be considered for selection as a lead.

At the meeting, Upjohn conveyed its view that low toxicity was far more important than extreme potency. Upjohn urged that the most important criterion for selection was the therapeutic ratio, that is, the difference between the effectiveness of the drug and the appearance of side effects. Due to its lack of

toxicity, Upjohn pressed for the selection of pioglitazone over far more potent compounds.

In the end, Takeda and Upjohn selected five compounds from Table 2 for further testing. Pioglitazone was among the five. None of the other four ended in a pyridyl ring, and none of the others emerged as a viable candidate for commercial development from the additional testing which followed.

The decisions reached at the October meeting were vitally important to both Takeda and Upjohn. Each company intended to spend millions of dollars and valuable research resources on the selected compounds. In addition, their scientists would be spending several years of their professional lives developing the chosen compound. Having experienced a significant set back with the failure of ciglitazone, Upjohn and Takeda were looking for a compound that would validate both their focus on TZDs and their use of the KKA^{y} mouse as an effective way to test the efficacy of compounds intended to treat diabetes. Development of a safe and efficacious molecule that could be successfully developed as a pharmaceutical would validate the years Takeda and Upjohn had invested in research.

O. Final Selection of Pioglitazone

Takeda and Upjohn continued their evaluation of the candidate compounds in late 1985 and early 1986. After more extensive toxicity studies, pioglitazone was chosen as the primary candidate for commercial development at a meeting between Upjohn and Takeda in Osaka on March 7, 1986. Pioglitazone met the im-

portant toxicity criteria: it was clean at 100 mg/kg/day in heart, liver and erythrocyte toxicity screening, as well as in the in vitro chick lens assay. Upjohn repeatedly confirmed pioglitazone's ED^{25} score.

Upjohn's decision to develop pioglitazone was not based on Takeda's data alone. Upjohn, under Colca's supervision, had conducted confirmatory efficacy and toxicity tests on over fifty of the TZD derivatives for which it received data from Takeda, including ciglitazone and pioglitazone, following experimental protocols identical to those described by Takeda in Report A-15-34. Upjohn's tests did not produce any results that were materially inconsistent with those reported to it by Takeda.

P. Prosecution History of the '777 Patent

In December 1984, Meguro submitted a request to file a patent application to Takeda's Central Research Library. The request, dated December 17, 1984, names Meguro and Fujita as joint inventors and identifies the structure of pioglitazone. The internal patent request only claims pioglitazone; there is no request to claim an ethyl substituent at any other position on the pyridyl ring.

On January 19, 1985, Takeda filed a Japanese priority patent application covering pioglitazone, and containing the efficacy and toxicity data presented in Table 1 of the '777 Patent. On January 17, 1986, Takeda filed the U.S. patent application covering pioglitazone. The substance of the application was virtually identical to the Japanese priority patent application.

The patent application included an Information Disclosure Statement ("IDS") which identified relevant prior art references as including the '200 Patent and Sohda II.

Takeda made six claims in its application. Claim 1 was for a compound of the formula:

Tabular or graphic material set at this point is not displayable.

or a pharmacologically acceptable salt thereof.

The right end of the molecule is the defining TZD structure. For our purposes, the critical part of the formula was the left-hand portion, which was the pyridyl ring with a C_2H_5 (or ethyl group) connected to the pyridyl ring by a line leading into the middle of the ring. Drawing a line into the center of the ring means that the ethyl group can be located on any open position on the pyridyl ring.

Claims 2, 3 and 4 are dependent claims which refer back to claim 1.[19] Claim 2 is for the compound in claim 1 with the ethyl group in the 5 position, that is, pioglitazone. Claim 3 is for the sodium salt of pioglitazone. Claim 4 is for the compound in claim 1 with the ethyl group in the 6 position. This compound has never been developed by Takeda.

Takeda's application states that the purpose of its invention "is to provide compounds which can be practi-

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[19] The application also included two claims that were later withdrawn.

cally used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." In support of its statement, Takeda provided efficacy and toxicity data on six compounds. The toxicity data are identical to the data presented in Report A-15-13. The efficacy data are identical to that contained in Report A-15-34.

The six compounds listed in the table are identified as (I), (a), (b), (c), (d), and (e). Compound (I) is pioglitazone. Compound (a) is ciglitazone, which has a different left end moiety than that in the other five compounds identified in the table. Ciglitazone has a methylcyclohexyl ring instead of a 2-pyridyl ring. Ciglitazone was disclosed in the prior art, having been specifically identified in both the '200 Patent and Sohda II.

Compounds (b), (c), (d), and (e) and pioglitazone each have a 2-pyridyl ring at the left end. Compounds (b), (c), (d), and (e) have a methyl at the 6, 5, 4, and 3 positions, respectively, on the 2-pyridyl ring. Pioglitazone has an ethyl at the 5 position. Compound (b) was also specifically identified in both the '200 Patent and Sohda II.[20] Compound. (c), which has the methyl in the 6 position, is the homolog of pioglitazone.[21] Table 1 of the '777 Patent is reproduced below:

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[20] As has been noted previously, compound (b) was compound 42 from the '200 Patent and compound 58 from Sohda II.

[21] The term homolog describes the relationship between two compounds that differ by the addition of a repeating group, usually a single CH_2 group. An ethyl group, C_2H_5, differs from a methyl, CH_3, by a single CH_2 group.

TABLE 1

Tabular or graphic material set at this point is not displayable.

Comparative data on compound (b) were included in Table 1 of the patent application because it is the closest prior art. Data on ciglitazone were included, despite its clinical failures, because it was the first TZD evaluated by Takeda to show potential for use as an anti-diabetic compound and had served as an index against which to compare new compounds. The application included data on the 3, 4 and 5-methyl variants of compound (b) because the compounds were structurally close to both pioglitazone and compound (b). They were also included to emphasize that the results for pioglitazone reported in Table 1 were "quite unexpected" even when compared to its homolog, compound (c).

Two errors were made in the section which describes the method by which Takeda tested for toxicity in rats. First, the application indicates that data on toxicity were obtained using Sprague-Dawley rats, when in fact the data were obtained from Wistar rats. Both are normal strains of rats and the same methods are used to test for toxicity in either strain. The error had no implications for the validity of the test results. In previous toxicology screens, the results of studies with the two species had been comparable.

The second error involved the age of the rats used in the testing. In the patent application, the age of the rats is listed as 5 weeks old when it should have been

listed as 5-6 weeks old. In the two-week toxicity tests reported in Table 1 of the '777 Patent, the results for pioglitazone were obtained from rats that were six weeks old at the beginning of the two week test; the results for the other compounds were obtained from rats that were five weeks old at the beginning of the two-week experiments. The data for all the compounds were normalized to body weight to account for variation in the size of the animals, and in each test the age of rats in the control group was the same as in the group receiving the compound. The one week age difference between the five and six week old rats did not affect the validity of the comparison.

On July 1, 1986, the examiner in charge of Takeda's U.S. patent application issued an office action ("Office Action") requesting an explanation of how to interpret the data presented in Table 1, particularly how to "balance the need for effective ED_{25} versus the need for lower toxicity." He rejected claims 1-5 under 35 U.S.C. § 112, quoting the section as follows:

> The specification shall contain a written description of the invention and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The Office Action also noted that Table 1 failed "to provide values for the control group." As a result of the lack of guidance on how to read the table, the Office Action pointed out that "one of ordinary skill is

not taught how to interpret the data and distinguish over the prior art." The Office Action requested guidance on whether there was a "therapeutic ratio" that could be used to compare the compounds and whether there was a threshold of "maximum toxicity." The Office Action concluded by asking "at what point is increased potency not desirable over increased toxicity? From the data provided one cannot conclude that [pioglitazone] is unexpectedly different from the rest."[22]

In response to the Office Action, Takeda submitted an amendment ("Amendment") and a declaration from Fujita ("Declaration"). The Amendment explained how to read Table 1, noting that the compounds (c), (d), and (e) were not disclosed in the prior art, but were tested because their chemical structure is similar to pioglitazone's. The Amendment explained how the ED^{25} values were calculated and the significance of the two-week toxicity testing in rats. It noted that only pioglitazone and compound (c) did not show any toxicity at a dose of 100 mg/kg/day for two weeks.[23] The Amendment calculated a "safety margin" for the different compounds, dividing the lowest toxic dose by the minimum effective dose. Noting that a compound with a higher safety margin is preferable, it argued that the test results showed that pioglitazone was "the most advantageous." The Amendment also ex-

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[22] The file history for the '777 Patent reflects that three examiners, each of whom was trained in chemistry, were involved in the prosecution. Their annotations to Sohda II and Table 1 show particular attention to prior art compound (b).

[23] As previously noted, pioglitazone and compound (c) are the only compounds in Table 1 with substituents at position 5 on the 2-pyridyl ring.

plained why it was "meaningless to show the values of the control" if one is skilled in the art.

In order to complete the safety margin calculations, Fujita's Declaration added calculations for rat triglyceride ED^{25} values for three compounds. These values were the only omissions in the columns of data presented in Table 1. Fujita asked his researchers to perform the experiments to generate the missing triglyceride ED^{25} data for compounds (c), (d), and (e). The report from the researchers who conducted the experiments showed ED^{25} data for two of the compounds but reported that compound (d) showed no effect. Fujita chose to take the ED^{25} rat triglyceride data for the third compound from Report A-15-34.

The experiments for rat triglyceride values for compounds (c) and (e) were performed by an experienced technician and supervised by an experienced researcher. During the experiment, the supervisor decided to exclude a control rat from consideration. It was common at Takeda to give researchers discretion not to use data from a single outlier animal.

Takeda filed its Amendment and the accompanying Declaration from Fujita with the PTO in November 1986. The PTO issued a Notice of Allowability on January 6, 1987. The patent issued on August 18, 1987. The '777 Patent was originally set to expire on January 17, 2006. The patent term was extended by five years to January 17, 2011, pursuant to a petition filed by Takeda under the Hatch-Waxman Act.

Q. Upjohn Abandons Pioglitazone

Upjohn ended its collaboration with Takeda in September of 1993. In doing so, Upjohn considered an upcoming "milestone" payment due to Takeda, its desire to leave the diabetes market, and its concern about litigation risks associated with launching a new drug. Upjohn management also had concerns about some of the results from longer term toxicity studies on pioglitazone. The Upjohn scientists most directly involved in supervising the development of pioglitazone disagreed with the decision and were deeply disappointed by it. Upjohn's decision contributed to the long delay between the '777 Patent issuing and the FDA approving ACTOS®, a delay which resulted in pioglitazone being the third TZD, instead of the first, to reach the U.S. market.

R. Combination Uses

Takeda has received seven patents for pioglitazone to be used in combination with other drugs ("Combination Use Patents"). All but one of the Combination Use Patents expire on June 16, 2016; one expires on August 9, 2016. As already noted, it is common for diabetics to be treated with several drugs at the same time, each targeting a different body mechanism associated with the disease.

S. Marketing ACTOS®

The FDA approved ACTOS® in July 1999. Before May 1998, Takeda had no wholly owned United States sales entity. Takeda North America was created in May 1998 to market ACTOS® in the United States. In preparation for the launch of ACTOS®, Takeda Pharmaceuticals America, Inc. ("TPA"), the

predecessor to Takeda North America, entered into a license agreement with Takeda which would allow Takeda North America to sell and market ACTOS® in the United States. TPA also entered into an agreement on December 14, 1998 with Eli Lilly and Company, which required Eli Lilly to co-promote ACTOS® with Takeda North America.

T. Hatch-Waxman Act [24]

The introduction of new drugs in the U.S. market is governed by the Federal Food, Drug and Cosmetic Act, which prohibits the introduction into interstate commerce of "any new drug, unless an approval of an application filed pursuant to subsection (b)" of 21 U.S.C. § 355"is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) describes the process of filing a New Drug Application ("NDA") with the FDA. The process of filing an NDA is typically costly and time-consuming. In the case of pioglitazone, for example, it took almost 12 years from the issuance of the '777 Patent until pioglitazone (in the form of pioglitazone hydrochloride) was approved by the FDA for the treatment of Type 2 diabetes on July 15, 1999.

In 1984, in order to accelerate the approval process for low-cost generic versions of established drugs, Congress enacted the Hatch-Waxman Act. Among other things, the Hatch-Waxman Act added subsection (j) to Section 355. Hatch-Waxman Act § 101. Subsection (j) provides for the filing of an Abbreviated New Drug Application ("ANDA") with the FDA

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[24]This treatment of the Hatch Waxman Act draws significantly from the description in *In re Tamoxifen Citrate Antitrust Litig.*, 429 F.3d 370, 374-77 (2d Cir.2005).

for the bioequivalent form of a drug already approved for safety and effectiveness. 21 U.S.C. § 355(j)(1), (j)(2)(A), (j)(7)(A). Subsection (j)(7)(A) further provides that the Secretary of the FDA will create and maintain a list of such approved drugs. *Id.* § 355(j)(7)(A). This list, *Approved Drug Products with Therapeutic Equivalent Evaluations,* is commonly known as the "Orange Book." *See id.;* http://www.fda.gov/cder/ob/default.htm.

When filing an ANDA, the filer must also include, with the application, "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug...." 21 U.S.C. § 355(b)(1). An ANDA filer must certify, with respect to each patent that claims the listed drug, either that no patent was filed for the listed drug (a "paragraph I" certification), that the patent has expired (a "paragraph II" certification), that the patent will expire on a specified date and the ANDA filer will not market the drug until that date (a "paragraph III" certification), or that the patent is invalid or would not be infringed by the manufacture, use, or sale of the new drug (a "paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii).

An ANDA filer that elects a paragraph IV certification must notify each affected patent owner of the certification. *Id.* § 355(j)(2)(B)(I). The patent owner then has forty-five days after the date it receives such notice to bring suit against the ANDA filer for patent infringement. *Id.* § 355(j)(5)(B)(iii). If no patent owner brings such a lawsuit during this period, the FDA may immediately approve the ANDA. *Id.* If, however,

the patent owner brings suit during this period, the FDA's final approval of the ANDA is stayed for thirty months after the date the patent owner received the requisite notice,[25] or until a district court returns a decision as to the validity of the patent or its infringement if it does so before the thirty-month period expires. *Id.*

ANDA applicants may also satisfy their obligation to address all relevant patents by filing a statement under 21 U.S.C. 355(j)(2)(viii) ("Section viii Statement"). By filing a Section viii Statement the applicant acknowledges that the drug sought to be manufactured is protected by a method of use patent, but claims that the applicant is not seeking approval for the patented use. An ANDA filer can submit either a Section viii Statement or a paragraph IV certification for each listed patent, but not both. *See Purepac Pharm. Co. v. Thompson,* 354 F.3d 877, 880 (D.C.Cir.2004).

Any approval letter sent by the FDA before the expiration of the prescribed stay and before a court ruling of patent invalidity or non-infringement is tentative. *See*21 C.F.R. § 314.105(d). If before the thirty months expire a court rules that the patent is either invalid or not infringed, the tentative approval of the ANDA is made effective as of the date of judgment. 21 U.S.C. § 355(j)(5)(B)(iii)(I). If after thirty months there has been no ruling on patent validity or infringement and the stay expires, the ANDA filer can distribute and

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[25] The notices of paragraph IV certification that Takeda received from Mylan and Alphapharm are dated September 8, 2003, and January 29, 2004, respectively. Thus, the 30 month periods will run on March 8 and July 29, 2006.

market the drug but, depending on the court's later patent ruling, an ANDA filer that chooses to follow this course may thereafter become liable for damages if infringement is found. *In re Tamoxifen*, 429 F.3d at 376.

As an incentive for generic manufacturers to choose the paragraph IV certification route, and thereby to challenge weak patents, the Hatch-Waxman Act offers under certain conditions, the first ANDA filer with a paragraph IV certification the opportunity to market its generic drug exclusively for 180 days. To this end, the FDA may not approve the ANDA of a subsequent filer until 180 days after the earlier of the date 1) the first ANDA filer commercially markets the generic drug, or 2) a court of competent jurisdiction concludes that the patent in question is invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II).[26]

Alphapharm was the first to file an ANDA. Its submission to the FDA was ultimately rejected because it could not make a pill that was a bioequivalent to ACTOS®.[27] As a result, the second filer, Mylan, will en-

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[26] Until 1998, the 180 day exclusivity period was available to the first ANDA filer to elect a paragraph IV certification only if it successfully defended a lawsuit for infringement of the relevant patent. *See*21 C.F.R. § 314.107(c)(1) (1995). This "successful defense" rule was challenged and rejected by circuit courts in two separate lawsuits. *See, e.g., Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1076 (D.C.Cir.1998). The FDA formally revoked the "successful defense" requirement in 1998. *See*Effective Date of Approval of an Abbreviated New Drug Application, 63 Fed.Reg. 59,710, 59,710 (Nov. 5, 1998), 21 C.F.R. § 314.107 (1999).

[27] It appears that the FDA rejected Alphapharm's ANDA at some point between its initial filing in July 2003, and its filing of a Section 355 Statement in January 2004.

joy the six month exclusivity period if the '777 Patent is invalidated.

U. The Defendants' ANDA Filings

On July 15, 2003, Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Danbury Pharmacal, Inc. ("Watson"), Alphapharm, Ranbaxy Laboratories, Ltd., and Ranbaxy Pharmaceuticals, Inc. ("Ranbaxy"), and Mylan all filed ANDAs seeking approval to market 15 mg, 30 mg, and 45 mg pioglitazone hydrochloride tablets. Ranbaxy and Watson filed paragraph III certifications with respect to the '777 Patent; they did not challenge its validity, representing instead that they will not make, use, sell, or offer for sale their products until the expiration of the '777 Patent. Both Ranbaxy and Watson also filed paragraph IV certifications relating to the composition claims in the Combination Use Patents.[28]

Alphapharm filed a paragraph IV certification claiming that the '777 Patent is invalid. Alphapharm filed a Section viii Statement with the FDA with respect to the Combination Use Patents, asserting that it does not seek approval for any of the uses covered by those patents.

Mylan filed a paragraph IV certification with respect to the '777 Patent, claiming that it is invalid. With respect to the Combination Use Patents, Mylan filed a paragraph IV certification addressing the pharmaceutical composition claims of one of the patents and

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[28]Ranbaxy also included, with its Paragraph IV certification, Section viii Statements with respect to the method claims contained in the Combination Use Patents.

a Section viii Statement regarding the method claims.

V. The Alphapharm and Mylan Statements of Obviousness

In their paragraph IV certifications, both Alphapharm and Mylan claimed that the '777 Patent was invalid due to obviousness. Alphapharm and Mylan were required to send a notice of paragraph IV certification that included detailed statements of the legal basis of their positions that the '777 Patent was invalid ("Section 355 Statement"). *See*21 U.S.C. § 355(j)(2)(b)(ii). By the time of trial, each defendant had radically altered the approach to the invalidity issue expressed in its statement. Mylan abandoned its articulated theory of obviousness in its entirety, and pursued an inequitable conduct claim at trial. Alphapharm altered its obviousness argument in several substantial ways. The following describes the parties' Section 355 Statements and compares them to the positions they took at trial.

Alphapharm's Section 355 Statement, dated January 29, 2004, recognized that it had the burden to prove by clear and convincing evidence that the prior art must provide some reason or motivation for a person of ordinary skill to make pioglitazone. It identified only two sources of prior art: the '200 Patent and Sohda II. As its position at trial evolved, it also argued that the divisional patents to the '200 Patent and a few articles in scientific journals were also prior art.

Insofar as the '200 Patent was concerned, Al-

phapharm argued in the Statement that the patent generically disclosed pioglitazone, and identified three compounds related to pioglitazone: compounds 16, 40, 42.[29] It noted that compound 42 is the methyl homolog of the ethyl compounds covered by Claim 1 of the '777 Patent, and argued that an exchange of an ethyl group for a methyl group would have been obvious.

Next, relying on the fact that two compounds discussed in Sohda II, compounds 11 and 14, are revealed in that article to have identical efficacy and yet differ only in that one has an ethyl substituent and another has a methyl substituent, Alphapharm contended that one of ordinary skill would conclude that the methyl and ethyl are "equivalent with respect to biological activity on a closely related analog of pioglitazone." In making this assertion, Alphapharm identified each compound as attached to a pyridyl ring. Neither compound has a pyridyl ring as its left end moiety and Alphapharm does not argue at trial that they do.[30]

At trial, Alphapharm concentrated on an entirely different compound described in Sohda II. It argued that the discussion in Sohda II of compound 58 (which had a higher combined efficacy score than either compound 11 or 14) would have led one of ordinary skill in the art to choose compound 58 as the lead compound for further development. That argument is not

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[29] Compound 16 has an ethyl substituent on a phenyl ring. Compound 40 is the unsubstituted pyridyl ring known as compound 3894. Compound 42 has a 6-methyl substituent on a pyridyl ring; it is compound (b).

[30] A benzene ring is at the left end of each compound.

to be found in Alphapharm's Section 355 Statement.

Alphapharm also argued in its Section 355 Statement that both the '200 Patent and Sohda II identify ciglitazone as having low toxicity, and that Takeda did not demonstrate that pioglitazone was surprisingly superior to ciglitazone. Similarly, it contended that the '777 Patent alleges an entirely different activity for ciglitazone than was disclosed in Sohda II. Alphapharm did not pursue either theory concerning ciglitazone at trial.

Next, Alphapharm's Section 355 Statement argued that Table 1 in the '777 Patent does not support the superiority of pioglitazone, and that the testing methodology described in the patent is flawed. Specifically, Alphapharm argued that "many" of the toxicity values on Table 1 were not "statistically significant." Alphapharm did not make this argument at trial.

Alphapharm argued in its Section 355 Statement that the experiments underlying the testing of a compound's toxicity to the heart were "inherently flawed" since Table 1 in the '777 Patent indicated that pioglitazone did not cause heart enlargement with a dose of 100 mg/kg, while the prescribing information for ACTOS® advises that heart enlargement was observed at 4 mg/kg in rats. The screening tests that produced the Table 1 data were, as described in the Patent's Application, two-week tests. The tests to which the ACTOS® disclosure refers were long-term tests conducted by Upjohn in 1992. Alphapharm tried to use this flawed post-hoc reasoning at trial, and that effort was rejected.

In its Section 355 Statement, Alphapharm next argued that the examiner should not have found that Takeda presented sufficiently compelling evidence to overcome the prima facie obviousness of pioglitazone. It pointed to the efficacy data for the rats, which showed that the ED^{25} values for all of the pyridyl ring compounds were comparable and that all have strong pharmacological activity. In a related argument, Alphapharm contended in its Section 355 Statement that Takeda did not present any data to the examiner to establish that the other three ethyl 2-pyridyl compounds covered by Claim 1 had surprising or unexpected results. At trial, the thrust of Alphapharm's evidence concerned compound (b), which Table 1 revealed was potent in both mice and rats, but highly toxic. Alphapharm did, however, particularly in its summation, try to fashion an argument about the ethyl compounds other than pioglitazone that are covered by the patent.

Mylan's Section 355 Statement, dated September 8, 2003, was far more straightforward. It also identified only two relevant pieces of prior art, the '200 Patent and Sohda II. It argued simply that one compound described in both, which had a benzene ring at the left end instead of a pyridyl ring, and which was identified in Sohda II as having high efficacy,[31] made the invention of pioglitazone obvious. According to Mylan, the two compounds are "bioisosteres," and their structural similarity made it obvious to replace a benzene ring with a pyridine ring.

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[31] The benzene compound is compound 16 in the '200 Patent and compound 14 in Sohda II.

Mylan incorrectly described the benzene compound both in terms of its structural relationship to pioglitazone and in terms of its efficacy.[32] In any event, Mylan completely abandoned this theory of obviousness during the discovery period. It proceeded to trial on an inequitable conduct claim.

W. Procedural History

On September 16, 2003, Takeda sued Mylan, Watson and Ranbaxy. Takeda sued Alphapharm on March 12, 2004. Takeda alleged direct infringement of the claims of the '777 Patent against Mylan and Alphapharm, and sought a declaratory judgment of induced infringement of the claims of the Combination Use Patents against all four defendants. Takeda's action against Alphapharm was accepted as a related to the other three actions on March 18, 2004. In their answers, Mylan and Alphapharm both asserted that the '777 Patent was invalid on the ground of obviousness. Defendant Watson moved to dismiss as nonjusticiable those claims in Takeda's complaint that alleged induced infringement of the Combination Use Patents. Watson's motion was denied because Takeda alleged "a controversy of sufficient immediacy." *Takeda Chem. Indus., Ltd. v. Watson Pharm., Inc.*, 329 F.Supp.2d 394, 403 (S.D.N.Y.2004). A July 20, 2004 Order set May 27, 2005 as the date by which fact discovery would end, and set January 16, 2006 as the trial date.[33]

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[32] The compound had a combined efficacy score of 5; many compounds had higher scores.

[33] The trial date was later moved to January 17, 2006, due to a federal holiday.

Alphapharm moved to dismiss nine of Takeda's claims relating to the Combination Use Patents on May 21, 2004. On the same day, Takeda moved to dismiss Alphapharm's affirmative defense and counterclaim for "patent misuse." Alphapharm's motion was denied by Order dated August 13, 2004. Takeda's motion to dismiss was granted in an Opinion that noted that Alphapharm had failed "to meet even the minimal requirements of notice pleading." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 04 Civ.1966(DLC), 2004 WL 1872707 (S.D.N.Y. Aug. 19, 2004).

Mylan's substitution of an inequitable conduct claim for its obviousness theory occurred in 2005. By letter dated March 15, 2005, Mylan noted that it could not locate experiments in Takeda's laboratory notebooks to support all the data submitted to the PTO and raised for the first time an argument that Takeda may have procured the '777 Patent "through inequitable conduct." On April 25, in response to a contention interrogatory from Takeda, Mylan formally contended for the first time that the '777 Patent was unenforceable on the basis that Takeda had committed inequitable conduct in its prosecution of the '777 Patent.[34] On June 6, after the close of fact discovery, Mylan served supplemental responses to Takeda's interrogatories, in which it expressed the view that the '777 Patent was invalid on the basis of obviousness

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[34]Despite this notice, in early June, Mylan's counsel refused to let the company's Rule 30(b)(6) witness explain the bases for Mylan's contention that the '777 Patent is invalid on grounds other than those disclosed in the Mylan's Section 355 Statement.

over compound 57 from Sohda II,[35] a different compound from the one identified in Mylan'sSection 355 Statement. Mylan's effort to substitute a new theory of obviousness was rejected in an Order of June 15. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2005 WL 1457696, at *2 (S.D.N.Y. June 15, 2005). *Seealso Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2005 WL 2092920, at *1 (S.D.N.Y. Aug. 31, 2005). Meanwhile, on June 15, Mylan was given leave to amend its answer to add a claim for inequitable conduct, essentially because of the "desire that issues, if at all possible, be addressed on the merits in litigation." *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 44053, at *1 n. 2 (S.D.N.Y. Jan. 9, 2006). Given its late notice of this new claim, Mylan was required to present all bases for the claim in its expert reports.

All four actions were consolidated for trial by Order dated October 13, 2005, although the '777 Patent issues were to be tried before the issues relating to the Combination Use Patents. By Order of December 30, 2005, the trial on the Combination Use Patents was severed.

Takeda, Alphapharm and Mylan moved *in limine* to strike testimony by or to preclude certain witnesses. Takeda moved against Mylan experts Hendry, Nusbaum, and Ronis. Alphapharm moved against Takeda experts Hendrickson, Inzucchi, Kettyle, Koller and Stoner. Mylan moved against Stoner and to exclude a supplemental declaration from Landau. Mylan also

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[35] Compound 57 is Takeda compound 3894, the unsubstituted 2-pyridyl.

moved to preclude Takeda from offering evidence of any missing laboratory notebooks.

Ronis' testimony was stricken to the extent it was not contained in his expert report. *Id.* at *2. Hendry's testimony was stricken to the extent it covered areas in which he had denied having expertise. *Id.* at *2-3. The motions addressed to testimony by Nusbaum and Stoner were granted to the extent they offered legal argument or opinions that went beyond their expertise. *Id.* at *3; *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 137374, at *2 (S.D.N.Y. Jan. 11, 2006). Landau's supplemental declaration was stricken. *Takeda*, 2006 WL 44053, at *3. Mylan's motion to exclude evidence of any missing notebooks was denied. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 83112 (S.D.N.Y. Jan. 12, 2006).

Hendrickson's testimony was stricken to the extent he opined on the selection of lead compound. *Takeda*, 2006 WL 137374. The motions concerning Koller, *id.* at *2, and Inzucchi and Kettyle were denied, *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253, 2006 WL 66480 (S.D.N.Y. Jan.12, 2006).

At trial Mylan offered into evidence the unredacted declarations from Hendry and Ronis that it had served with the Joint Pretrial Order. The unredacted Ronis declaration was submitted as an Offer of Proof pursuant to Rule 103 of the Federal Rules of Evidence. In making its Offer of Proof, Mylan emphasized that it was not seeking to make a motion for reconsideration of the Court's decision to strike parts of Ronis' testimony, *Takeda*, 2006 WL 44053, and it is

not being treated as such.[36]

Discussion

Alphapharm asserts that pioglitazone is obvious in light of the prior art. Mylan contends that Takeda engaged in inequitable conduct. For the following reasons, each of these arguments is rejected.

I. Obviousness

Inherent in the Constitution's grant of patent power to Congress is the requirement that a patent monopoly be conveyed only where there is "[i]nnovation, advancement, and things which add to the sum of useful knowledge." *Graham v. John Deere Co.*, 383 U.S. 1, 6, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Through the 1952 Patent Act, Congress codified three conditions for patentability: novelty, utility, and non-obviousness. *Id.* at 17, 86 S.Ct. 684; 35 U.S.C. § 101-103. It is the last of these three conditions on which Alphapharm rests its challenge to Takeda's '777 Patent.

A patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that *the subject matter as a*

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[36] At trial, Takeda presented its evidence first. At the close of Takeda's case on January 25, both Takeda and Alphapharm moved for judgment as a matter of law under Rule 52(c). Fed.R.Civ.P. 52(c). Alphapharm had not carried its burden of showing obviousness at that point, and did not do so either through its later presentation of its own evidence. Since the burden rested on Alphapharm, it was not appropriate to grant Takeda's motion until Alphapharm had had an opportunity to present its case.

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (emphasis supplied). Section 103 emanates from the Supreme Court's nineteenth century decision in *Hotchkiss v. Greenwood,* 52 U.S.(11 How.) 248, 13 L.Ed. 683 (1850), and its progeny, which took a functional approach to patent analysis and eschewed labels. *Graham,* 383 U.S. at 12, 17, 86 S.Ct. 684. The talismanic statement of the obviousness inquiry appears in *Graham,* which identifies four factual underpinnings to a determination of obviousness: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claimed invention, and (4) objective indicia of non-obviousness. *Id.* at 17-18, 86 S.Ct. 684; *see Merck & Co., Inc. v. Teva Pharm. USA, Inc.,* 395 F.3d 1364, 1372-73 (Fed.Cir.2005). The issue of obviousness is a question of law. *Richardson-Vicks Inc. v. Upjohn Co.,* 122 F.3d 1476, 1479 (Fed.Cir.1997).

The scope and content of the prior art includes art that is "reasonably pertinent to the particular problem with which the invention was involved." *Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 664 (Fed.Cir.2000) (citation omitted). Prior art must be available before the date of invention. 35 U.S.C. § 103(a), *see Richardson-Vicks Inc.,* 122 F.3d at 1480. Prior art teaches away from an invention "when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.,* 407 F.3d 1371, 1380 (Fed.Cir.2005).

Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. *Ruiz*, 234 F.3d at 666. In determining what constitutes ordinary skill in the art, a court may consider "1) the types of problems encountered in the art; 2) the prior art solutions to those problems; 3) the rapidity with which innovations are made; 4) the sophistication of the technology; and 5) the educational level of active workers in the field." *Id.* at 666-67.

Secondary considerations or the objective indicia of non-obviousness include "commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." *Id.* at 662-63. These considerations are probative to the extent they "give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18, 86 S.Ct. 684. The "nexus" or causal relationship between the secondary consideration and the claimed invention should shed light on whether the invention was obvious or not. *See Merck*, 395 F.3d at 1376. A presumption that a patented invention is commercially successful arises when a patentee can demonstrate "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1377 (Fed.Cir.2000) (citation omitted).

Patents are presumed to be valid. 35 U.S.C. § 282. A party challenging a patent can establish a prima facie case of invalidity by showing that the invention is obvious under an analysis of the first three *Graham* factors. *Winner Intern. Royalty Corp. v. Wang*, 202

F.3d 1340, 1350 (Fed.Cir.2000). If a prima facie case of obviousness is established, the burden of production shifts to the party defending the patent to demonstrate non-obviousness under the fourth *Graham* factor. *Id.* The burden of persuasion, by clear and convincing evidence, always remains with the party asserting the invalidity of the patent. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 725 (Fed.Cir.2002). The burden is "especially difficult" if the challenger relies on prior art "that was before the patent examiner during prosecution." *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed.Cir.2004) (citation omitted). This added burden stems from the "deference that is due to a qualified government agency presumed to have properly done its job." *Ultra-Tex Surfaces, Inc. v. Hill Brothers Chem. Co.*, 204 F.3d 1360, 1367 (Fed.Cir.2000) (citation omitted).

A strand of the law of obviousness addresses patents protecting chemical compounds. In the case of a chemical compound, a prima facie case of obviousness exists where there is a "structural similarity between claimed and prior art subject matter" and "the prior art gives reason or motivation to make the claimed compositions." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed.Cir.2000) (citation omitted). "[O]bviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention." *Beckson*, 292 F.3d at 727. Thus, an invention is prima facie obvious where the prior art would imbue one of ordinary skill in the art with a "reasonable expectation of success" in achieving the goals that the inven-

tor sought to accomplish by transforming a compound in the prior art into the structurally similar claimed invention. *Yamanouchi,* 231 F.3d at 1343 (citation omitted). While a reasonable expectation of success must be shown, in order to show prima facie obviousness it is not necessary to show that success was absolutely predictable. *Id.*

Where the creation of a chemical compound requires the chemist to pursue several steps in manipulating a compound revealed in the prior art, the patent challenger must show that one of ordinary skill in the art would have had sufficient motivation to take each of those steps. *Id.* at 1344-45. Similarly, if the prior art "offers no suggestion to pursue the particular order" of manipulations that led to an invention, and where a deviation in the order would have taught away from the invention, then the challenger must show what would have led any ordinary artisan in the field "to follow the precise steps that produced a remarkable invention." *Id.* at 1345.

A prima facie case of obviousness may be rebutted by "showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *Dillon,* 919 F.2d at 692-93. When rebuttal evidence is submitted, "all the evidence must be considered anew." *In re Eli Lilly and Co.,* 902 F.2d 943, 945 (Fed.Cir.1990); *see also Glaxo Group Ltd.,* 376 F.3d at 1349; *Richardson-Vicks,* 122 F.3d at 1482-83.

Alphapharm contends that pioglitazone is prima facie obvious over the prior art compound (b) from Table 1 of the '777 Patent, which had been identified in both

the '200 Patent and Sohda II. Alphapharm argues that the prior art clearly identified compound (b) as a lead compound warranting further investigation, and that the application of a few, obvious chemical processes would have produced pioglitazone. Turning to objective evidence of pioglitazone's obviousness, Alphapharm contends that pioglitazone's lack of toxicity is not unexpected because variability among compounds is "inherent". As for its commercial success, Alphapharm argues that the success of ACTOS® must be discounted because *inter alia* pioglitazone was not the first TZD on the market and is not the only successful TZD still on the market. These and Alphapharm's other arguments are described in detail below.[37]

Alphapharm's arguments fall woefully short of the mark. The prior art did not disclose or suggest either the pioglitazone molecule itself or how to make it. Alphapharm has not shown by any persuasive evidence, much less by clear and convincing evidence, that one with ordinary skill in the art would have had any reasonable expectation based on the prior art that synthesizing pioglitazone would result in the discovery of a non-toxic, effective treatment for diabetes, and therefore would not have had any motivation to do so. To begin with, the evidence is overwhelming that one skilled in the art would not have, based on the prior

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[37] It has been challenging to capture Alphapharm's arguments because it has presented a constantly shifting set of arguments, abandoning some, inventing others, and even contradicting itself as the trial progressed. Nonetheless, every effort has been made to address each of the principal arguments raised during the trial by Alphapharm.

art, chosen compound (b) as a lead compound. Beyond that, Alphapharm has not shown that the ordinary artisan would have had sufficient motivation to take each of the several conceptual and experimental steps that were necessary to move beyond compound (b) and create the pioglitazone molecule.

Even if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected. Alphapharm is unable to overcome the extreme differences in the toxicity profiles between pioglitazone and prior art compound (b), whose modification it contends would have led to the discovery of pioglitazone. Confronted with overwhelming evidence that the non-toxicity of pioglitazone was entirely unexpected given the high toxicity of compound (b), including the admission of Alphapharm's own expert that there was no reasonable basis to expect that pioglitazone would be non-toxic, Alphapharm ignores the relevant legal standard and argues simply that there is so much variability in the pharmacological effects of compounds, even compounds that share similar structures, that a compound's non-toxicity is "not surprising." This does not carry Alphapharm's burden of showing obviousness. The discussion that follows examines each of the Graham factors, paying particular attention to the identification of a lead compound, the motivation to alter that compound, and unexpected results.

A. Qualifications of a Person of Ordinary Skill in the Art

The parties agree that a person with ordinary skill in

the art would have a graduate degree in chemistry or a relevant branch of chemistry and practical experience applying that education by working at or consulting with a pharmaceutical company in the development of pharmaceutical compounds.[38] It is unnecessary to refine further the minimum qualifications of a person with ordinary skill in the art, since nothing that follows in this analysis turns on the presence of a more precisely drawn definition.

Alphapharm has argued that one of Takeda's experts, Danishefsky, is not qualified to opine about what one with ordinary skill in the art of medicinal chemistry would understand or do since he is a synthetic organic chemist. Danishefsky is a renowned synthetic organic chemist who has devoted his entire career to exploring the issues of medicinal chemistry.[39] He supervises the training of medicinal chemists, has recently been nominated to receive a lifetime achievement award in chemistry from a major pharmaceuti-

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[38] Alphapharm defines someone of ordinary skill in the art as a person who would have secured a Ph.D. in medicinal chemistry or a related field, done postdoctoral work for two to three years and thereafter worked for a pharmaceutical company for two to three years. Takeda defines the person as someone with a Master's Degree in chemistry or chemical engineering with four years experience in the research and development of pharmaceuticals or medical organic compounds, or someone with a Ph.D. in chemistry or chemical engineering with two years of experience in the research and development of pharmaceuticals or medicinal organic compounds.

[39] Takeda brought to this trial experts of extraordinary accomplishment and distinction. Many of them, including Danishefsky, were preeminent in their field of endeavor. These were scientists whose knowledge and opinions were uniformly helpful to the Court in understanding the science at issue here.

cal company,[40] and regularly consults with major hospitals and pharmaceutical companies on issues of medicinal chemistry. He is superbly qualified to opine in the field of medicinal chemistry.

B. Relevant Prior Art

As noted above, Takeda applied in Japan for what became known as the '777 Patent in January 1985, and in the United States in January 1986; the '777 Patent issued on August 18, 1987. It is undisputed that the relevant prior art for the '777 Patent includes the '200 Patent, issued in 1981; and Sohda II, published in 1982, both of which were identified by Takeda in its application for the '777 Patent. The '200 Patent first disclosed the compound on which Alphapharm relies for its obviousness argument, compound (b).[41] Alphapharm's expert identifies Sohda II as the "key" piece of prior art on which the skilled artisan would have relied to identify compound (b) as the lead compound for further investigation.[42]

Although Alphapharm's Rule 30(b)(6) witness testified that Alphapharm was not aware of any prior art that Takeda failed to put before the examiner, at trial Alphapharm identified two additional patents and

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[40] Danishefsky will receive a lifetime achievement award from Bristol-Myers Squibb in May 2006 and the National Academy of Science's medal in chemical sciences in April 2006.

[41] Compound (b) from Table 1 is a 6-methyl, which was identified in the '200 Patent as compound 42.

[42] While Alphapharm began the trial by identifying Sohda II as the critical writing which would have led one skilled in the art to identify compound (b) as a lead compound, in the face of overwhelming evidence to the contrary, by the end of the trial it had virtually abandoned reliance on Sohda II.

one other article as prior art. It asserts that two divisional patents for the '200 Patent, the '605 and '779 Patents, issued on July 20, 1982, and April 24, 1984, respectively, and their prosecution histories, should also be considered relevant prior art.[43] In particular, it asserts that the prosecution history of the '779 Patent, which was available to the public through examination in Washington, D.C. when the '779 patent was issued, would have assisted those with ordinary skill in the art in selecting compound (b) as a lead compound for further investigation. Finally, Alphapharm identifies an article in a peer reviewed scientific journal: Nohara, A. et al., "Studies of Antianaphylactic Agents. 6.1 Synthesis of Some Metabolites of 6-Ethyl-3(1H-tetrazol-5-yl) chromone and their Analogues," *Journal of Medicinal Chemistry,* 22:3, 290-295 (1979) ("Nohara Article").[44] Mosberg gleaned from the Nohara Article that persons of ordinary skill in the art, including Takeda, practiced the synthesis of routine homologs to improve promising drug compounds as of 1979.

C. Differences Between the Prior Art and Pioglitazone

Alphapharm's assertion of obviousness rests on two

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[43] Takeda disputes that these patents can properly be considered prior art.

[44] Alphapharm has abandoned its contention that a second article, Cunningham, S. et al., "The Characterization and Energetic Potential of Brown Adipose Tissue on Man", *Clinical Science* 69, 343-348 (1985) ("Cunningham Article"), was prior art. Alphapharm's expert used the Cunningham Article to educate himself about how persons of ordinary skill viewed the issue of brown fat in the 1980's. Compound (b) was identified in Sohda II as increasing brown fat.

claims: that it would have been obvious to select a single compound from the prior art-a 6-methyl on a pyridyl ring, which is compound (b) on Table 1 of the '777 Patent-as the "lead compound" for development, and that it would have been obvious to create and test the compounds that lie between the 6-methyl and pioglitazone, which is a 5-ethyl on a pyridyl ring.[45] The program would have entailed synthesizing compounds in which a methyl appears at each of the open positions on the pyridyl ring, a process that Alphapharm terms "walking the ring", and also synthesizing compounds in which the substituent on the pyridyl ring at each of these positions is an ethyl instead of a methyl, a process referred to as "homologation".

The following diagrams of the left end of compound (b) and pioglitazone illustrate the changes in the molecular structure that were necessary to make the transformation.

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Both of these structures are on a pyridyl ring.[46] Compound (b) has a substituent added at the 6th position on the ring; pioglitazone's substituent is added at the 5th position, counting counter-clockwise from the ni-

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[45] As already noted, a methyl group contains one carbon, while an ethyl group contains two carbons.

[46] For ease of reference, certain explanations are repeated here. Pyridyl denotes a six-membered ring of five carbon atoms and one nitrogen atom. The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion.

trogen atom on the ring.

1) Identification of a Lead Compound

Alphapharm's obviousness argument relies in the first instance on its contention that one skilled in the art wou'd have recognized compound (b) as the lead compound for further development.[47] Alphapharm's expert has rested his identification of compound (b) as a lead compound on his reading of the '200 Patent and Sohda II.

As described above, the '200 Patent provided protection for TZD derivatives. The molecular structure of compound (b) was illustrated in the patent as one of fifty-four examples of TZD compounds with a certain structure that had been synthesized through steps described in the patent. Examples of still more TZD compounds synthesized through other procedures were also illustrated. The prosecution history of the '200 Patent includes some test results for nine compounds that were presented to the PTO as "typical" of compounds covered by the disclosed invention in order to demonstrate that TZD compounds covered by the invention were "far superior" in their blood glucose and plasma triglyceride lowering effects than compounds in the prior art. Compound (b) was one of the nine whose test results were charted, and it was one of three such compounds charted in the '200 Pat-

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[47] Alphapharm's Section 355 Statement did not explain why compound (b) would be chosen as a lead compound over others described in either the '200 Patent or Sohda II. Alphapharm has abandoned its assertion in its Section 355 Statement that pioglitazone was obvious based on an analysis of compounds 11 and 14 in Sohda II.

ent that had the best disclosed performance.[48]

Since Takeda only presented test results for nine of the hundreds of millions of TZD compounds covered by the patent application, one with ordinary skill in the art would have had no reasonable basis to conclude that these nine were the best performing of all of the compounds tested by Takeda, and thus that one of these nine should be selected as the lead compound for further development. Even if one could make that leap, however, the prosecution history for the '200 Patent disclosed two other compounds, in addition to compound (b), that appeared to have superior performance among the nine that were tested. And, the next year, when Sohda II was published, compound (b) was not singled out as one of the best performing compounds.

Sohda II, which has also been described above, reported test results on 101 TZD compounds, and identified three that "exhibited the most favorable properties in terms of activity and toxicity." Each of these three compounds had a different left moiety, and therefore, provided different starting points from which one of ordinary skill in the art could make changes in the hope of identifying successful compounds. Compound 47 terminated with an unsubstituted cyclohexane ring[49] and is connected to the rest of the compound by a CH^2. Compound 49, which is ciglitazone, has a similar structure to compound 47, however, there is methyl substituent at the point of attachment to the rest of the compound. Compound

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[48]Of the nine, three compounds, including compound (b), had a combined score of 7; five had a score of 6; one had a score of 2.

[49] A cyclohexane ring is a saturated ring of six carbons.

59 is the only one of the three with a pyridyl ring at the left end moiety, however, it is a 3-pyridyl ring. (Pioglitazone's pyridyl ring is a 2-pyridyl ring.[50]) The following diagrams illustrate the differences in the left end of these structures more effectively than a narrative description.

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Compound (b) was among the 101 whose test results were reported in Sohda II, but it was *not* one of the three compounds identified by the authors as having the most favorable performance.

Sohda II gave detailed efficacy data, but did not set out the toxicity test results in comparable chart form. It did discuss in its narrative sections, however, various toxicity and side effect issues which eliminated some of the compounds with strong efficacy ratings from being singled out for their overall performance. For example, seven compounds had the highest combined efficacy score, which was a rating of 7. Sohda II identified problems with toxicity or side effects for six of the seven compounds.[51] Compound (b) was one of the seven, but was described as causing "considerable

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[50] The 2-pyridyl is attached to the remainder of the TZD molecule at the second position on the pyridyl ring; the 3-pyridyl, at the third position.

[51] The one compound that scored 7 and yet had no identified problems was compound 99. Its structure at the left end moiety differs significantly from the pyridyl.

increases in body weight and brown fat weight."[52] The three compounds that were identified as having the most favorable performance each had a combined efficacy score of only 5.[53]

A person with ordinary skill in the art would had concluded from an examination of the '200 Patent, including its file wrapper, and of Sohda II, that the three compounds identified in Sohda II as promising should be the starting point for further investigation. There were literally thousands of different substituents that one of ordinary skill in the art could consider in modifying those three compounds. Such a person would certainly not have concluded that compound (b) should be chosen as a lead compound over the many other more obvious or at the very least similarly interesting choices presented by that prior art. Indeed, Sohda II teaches away from compound (b) when it specifically comments on its negative effects on body weight and brown fat. Type 2 diabetes is a chronic disease. Any effective drug will be given over a long period of time, and therefore, those of ordinary skill in the art would have been especially sensitive to toxicity and side-effects.

History confirms this analysis. Takeda and another pharmaceutical company worked extensively to develop one of the three compounds identified by Sohda II as particularly promising, before abandoning it be-

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[52] Compound 3894, which had a combined potency score of five, was described as having the same problematic side effects as compound (b).

[53] Of the 101 compounds in Sohda II, 39 had a combined score of 5 or higher. Twenty-nine of the thirty-nine had been described in the '200 Patent.

cause of its toxicity. Ciglitazone was Sohda II's compound 49, and was withdrawn by Takeda from further development during human testing both because it failed the chick lens assay test and due to efficacy concerns.

In fact, because of concerns over toxicity in treating a chronic disease like diabetes, one skilled in the art would have been more likely to choose as a starting point for further research one of the many compounds in Sohda II, and there were over ninety, where the authors did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, than to choose as a starting point a compound with identified adverse effects. If for some yet unexplained reason one chose to start with a compound that had identified problems, one skilled in the art would be motivated to make fairly radical changes to it in order to try to overcome the problems.

Admissions from an Alphapharm scientist confirm that there was no basis to select compound (b) (that is compound 58 from Sohda II) as a lead compound other than hindsight. At his deposition, Rosenberg, who is the head of Alphapharm's intellectual property department and who was also the scientist who formulated its Section 355 Statement, admitted that there was "nothing to recommend" compound (b) over any of the other compounds that had a combined score of 7, and that he only chose compound (b) from Sohda II "because it was similar to pioglitazone."

During his cross-examination, Alphapharm's expert Mosberg presented a new and remarkable explana-

tion for why compound (b) would have been selected as the lead compound by one of ordinary skill in the art over the other six compounds with a rating of 7 and over the three compounds singled out for favorable mention in Sohda II. He argued that it appeared from Sohda II that each of these other compounds, and the molecules closely related to them, were being pursued actively by Takeda and that it would be impractical to compete with Takeda, given its head start, and to invest precious research resources into the compounds Takeda was investigating. This argument was not presented by Mosberg in his direct testimony, where he essentially ignored the existence of the other compounds that scored 7 and the three compounds given prominence in Sohda II. It also directly contradicts his direct testimony, where he asserted that compound (b) would have been selected as a lead compound by one skilled in the art because of the evidence that Takeda was "zeroing in on substituted pyridyl rings."[54]

In any event, there are a myriad of problems with Mosberg's recently invented analysis. First, it is not supported by any intellectually rigorous analysis. Second, the test is not whether a compound seems an unpopular candidate for development among competitors but rather whether one of ordinary skill in the art would have been motivated to choose it as a lead compound in an effort to develop a safe and effective drug to treat diabetes. Third, Mosberg's

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[54] Mosberg's trial testimony also directly contradicts Alphapharm's proposed findings of fact submitted before trial, which indicate that it hoped to establish that one skilled in the art would have understood that Takeda was focusing its attention on compound (b).

analysis completely undercuts Alphapharm's contention that compound (b) was the obvious lead compound for investigation. Surely, under Mosberg's revisionist reading of Sohda II, the compounds in which Takeda seemed to be expressing an interest were the more appropriate choices for one skilled in the art who was seeking to find a successful anti-diabetic agent, instead of compound (b), which he believes Takeda had abandoned.

Mosberg also tries to transform its identified problems of an increase in body weight and brown fat into an advantage for compound (b). He argues, with some creativity but little persuasion, that these identified problems would only "motivate one of skill in the art to make changes" in the compound.[55] Such a response does not explain, however, why compound (b), with its associated problems, should be chosen as the lead compound for further investigation.

Mosberg makes two other arguments in an effort to explain why compound (b) would be selected as a lead compound. First, Mosberg argues that further support for focusing on compound (b) comes from the '779 Patent, which specifically claims over sixty com-

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[55] It is undisputed that weight management is an important element in the treatment of Type 2 diabetes and that this was understood in the 1980s. Takeda's expert opines persuasively that the Cunningham Article, which warned that "considerable caution" should used in extrapolating animal studies' brown fat findings to humans, would not have diminished the negative impact of the statements about weight gain in Sohda II on a scientist evaluating compound (b) for exploration. Mylan's Rule 30(b)(6) witness opined that one of ordinary skill in the art would rule out compound (b) as a compound of interest because of its negative profile disclosed in Sohda II.

pounds including compound (b). Alphapharm's Section 355 Statement did not identify the '779 Patent as relevant prior art.

As already described, it was the PTO's initial rejection of the '200 Patent that led Takeda subsequently to file the '605, '779, and '141 divisional patents. Because they are divisional patents, the text of each of the divisional patents is identical to the text of the '200 Patent. The '200 Patent discloses hundreds of millions of TZD compounds. The divisional patents are directed to subsets of those compounds covered by the generic disclosure in the '200 Patent.The '779 Patent, which was filed after the '605 Patent, actually claims a larger class of compounds than the '605 Patent. The '605 Patent claims 1080 compounds, while the '779 Patent claims over one million compounds.[56] These patents claimed not only pyridyl derivatives but also thiazolyl derivatives.

Takeda filed the application for what became the '779 Patent on March 15, 1983, identifying through supporting diagrams over 60 compounds that were TZD derivatives. Essentially, the claims were directed to a structure with a pyridyl or a thiazolyl group at the left end of the TZD molecule, with one to three substituents on those rings, the substituents being selected from lower alkyls, halogens and hydroxyl. Two compounds were specifically claimed, compound (b) and a thiazolyl.[57] Compound (b) was also diagramed as compound 42 on the application. In a preliminary amendment of the same date, Takeda stated, "the

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[56] These numbers do not include the salts and stereoisomers covered by the patents.

[57] The thiazolyl was a 4-methyl 5-thiazolyl.

compounds in which these heterocyclic rings are substituted have become important, especially Compound 42."

There are several problems with Alphapharm's reliance on the '779 Patent.[58] Takeda's expert has given compelling evidence that medicinal chemists do not consider arguments made by patent counsel, particularly when there is contrary information in peer-reviewed literature (such as Sohda II), and that he has never known anyone in his over forty years of work in the field of medicinal chemistry to establish research priorities in this way. Alphapharm's expert essentially agreed, and Alphapharm has presented no evidence to the contrary.[59]

Moreover, if Alphapharm wishes now to rely on a divisional patent as prior art to explain why one skilled in the art would select compound (b) as a lead compound, then it is necessary to consider what one skilled in the art would have concluded by an examination of each of the Takeda TZD patents that had issued by this time. Taken together, they show that Takeda was actively conducting research in many di-

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[58] Alphapharm may also be attempting to make an inequitable conduct argument concerning the presentation of the toxicity data for compound (b) in the '777 Patent by comparing it to general statements in the '779 Patent about toxicity levels in TZD derivatives. The comparison is spurious and does not require further discussion.

[59] In addition, the file wrapper for the '779 Patent was simply not accessible to one of ordinary skill in the art. As of 1983, patent applications were not prosecuted publicly and the application would not have been available to the public until the patent had issued on April 24, 1984. At that time, the file history would have had to be specially obtained at the patent office.

rections, and had not narrowed its focus to compound (b).

Finally, in support of Alphapharm's argument that compound (b) would have been selected as the lead compound from the prior art, in particular from Sohda II, Mosberg contends that one of ordinary skill in the art would have observed that the four compounds revealed in Sohda II with a pyridyl ring on the left hand side of the structure, display high potency and that of those compounds the compound with the methyl substituent, that is compound (b) or 58, had the highest potency. He points with emphasis to the fact that the substituted pyridyl has a higher combined efficacy score than the unsubstituted pyridyl.[60] From that, Mosberg suggests that one of ordinary skill in the art would have concluded that the methyl substituent was responsible for increasing potency and thus would have been strongly motivated to attempt further substituent replacement to reduce the unwanted side effects of the 6-methyl, while maintaining its potency.

This argument benefits entirely from hindsight. Sohda II describes several clusters of efficacious compounds, including the cluster into which compounds 47 and 49 fall, compounds 47 and 49 being two of the three compounds given particular attention by the authors. In any event, of the cluster into which compound (b) falls, the most obvious candidate for a lead compound is the one identified by the article for further investigation, that is compound 59, since the ar-

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[60] The unsubstituted 2-pyridyl (compound 57) had a combined score of 5, while the 2-pyridyl with a methyl at the 6 position (compound 58) had a combined score of 7.

ticle reported no toxicity or harmful side effects for that compound. Exploration of that compound, which has a 3-pyridyl ring at its left end rather than the 2-pyridyl ring shared by pioglitazone and compound (b), would of course have led in a different direction.[61]

In sum, Alphapharm has failed to show that compound (b) would have been understood by one skilled in the art as a lead compound. There is no support for such a finding based on the prior art that Alphapharm identified in its Section 355 Statement: the '200 Patent and Sohda II. Thus, it now turns to a statement about compound (b) in application for the '779 Patent. One skilled in the art would not have relied on that reference to identify compound (b) as a lead compound given the more exhaustive and reliable scientific analysis presented by Sohda II, which taught away from compound (b), and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 Patent showing that there were many promising, broad avenues for further research.

2) Motivation to Create Pioglitazone

Assuming that compound (b) would have been identified by one skilled in the art as a lead compound, Alphapharm has not shown that such a person would have been motivated to synthesize the compounds that had to be created to find pioglitazone. First, one skilled in the art would have done an initial screen-

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[61] At his deposition Mosberg admitted that one skilled in the art would have been led to investigate all of the compounds based on the 2-, 3-, and 4-pyridyl ring, with less emphasis on the 4-pyridyl compounds.

ing of compound (b) for toxicity and concluded that its toxicity made it an extremely poor candidate for modification.[62] The likely course of action at that point, would have been to return to the compounds actually identified in Sohda II as worthy of further research.[63] Second, Alphapharm has failed to point to anything in the prior art that would have presented one skilled in the art with a reasonable expectation of success in creating the compound that became pioglitazone.

Before addressing Alphapharm's specific arguments, it is useful to describe briefly some of the pertinent chemistry and research issues that one skilled in the art would have faced in the 1980s. Many of the tools that assist today in the process of chemical synthesis were not available in the 1980s. At that time, the process of discovering new compounds for pharmaceutical development involved the screening of sample collections, usually those already in the libraries of the pharmaceutical company, or those created by the chemistry laboratories of the company. When a lead compound was identified, a lead compound being one that contains suggestive properties that are indicative of possibilities for progress, the scientist would modify the lead compound to achieve the right

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[62] As indicated on Table 1 to the '777 Patent, compound (b) was extremely toxic to the liver, heart, and blood.

[63] There is no contention that the investigation of the three compounds identified in Sohda II as worthy of further investigation would have led with sufficient directness to pioglitazone. As already noted, among other things, two did not have a pyridyl ring on the left moiety, and the left moiety in the third was a 3-pyridyl ring rather than the 2-pyridyl ring in the pioglitazone molecule, meaning that its attachment to the remainder of the TZD molecule was from a different point on the pyridine ring.

balance of potency and non-toxicity. The modification process was not routine. The chemistry laboratories of the company needed to create, through chemical synthesis, each new compound that needed its potency and toxicity tested. The conceptual acts of moving a methyl substituent to another position on a ring and of replacing it with an ethyl substituent require different starting materials and different chemical processes. While it may be easy to describe in English, the science is time-consuming.

The left-hand end of the TZD molecule is known as a terminating region, and is a so-called hot spot, where small changes can have dramatic repercussions in performance. It would have been a significant research project to understand the consequences of even small modifications to this region of the molecule, and one skilled in the art would not have had any reasonable basis to expect that even small changes in this area would result in an increase as opposed to a decrease in either the efficacy or toxicity of the molecule in any particular organ or body system much less in the body as a whole. There was absolutely no basis whatsoever to form a belief that any particular modification would change a toxic molecule into a non-toxic compound. There was simply no scientific literature which explained how the particular changes to a molecule that are at issue here would lead to a drug with particular effects, whether for better or worse, in the body. As of the 1980s, and even today, the actual mechanism through which a TZD molecule interacts with the body's processes is not understood. In the 1980s, for instance, scientists did not know the shape of the insulin receptor or the specific molecular target for the TZD compound.

Predicting toxicity based on the structure of a compound is particularly difficult. And, in selecting a lead compound for development of a drug to treat a chronic disease, one skilled in the art would have been particularly sensitive to issues of toxicity. As a result of all of these challenges, it is not uncommon to synthesize thousands of compounds before arriving at a new drug that survives all review and enters the pharmaceutical market in the United States. Alphapharm's expert estimates that, even when one has identified a lead compound, success is achieved in at most 1% of research projects.

Alphapharm's expert, Mosberg, argues that the twin steps of "walking the methyl around the ring" and "homologation" to create an ethyl from a methyl are routine steps in the drug optimization process that would have been performed by one of ordinary skill in the art and would have led quite directly to the discovery of pioglitazone from the investigation of compound (b). Mosberg's opinion was completely undermined by the other evidence presented at trial, including the far more credible testimony from Takeda's experts. It was also contradicted by Alphapharm's in-house medicinal chemist whose deposition testimony was partially adopted as Rule 30(b)(6) testimony for Alphapharm.[64] Rosenberg testi-

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[64] Alphapharm had identified Rosenberg as one of its trial experts, and had served his expert report. After he was deposed, however, Alphapharm withdrew its offer of Rosenberg as an expert at trial. Before making that decision, Alphapharm had adopted portions of Rosenberg's deposition testimony as evidence given by Alphapharm pursuant to Rule 30(b)(6), Fed.R.Civ.P.

fied that in making changes to the pyridyl ring on the left end of the TZD molecule, one would look at a host of substituents, such as chlorides, halides and others, not just methyls. He did not even mention ethyls.

a) Walking the Ring

Nothing in the prior art teaches that changing the position of the methyl substituent on the pyridyl ring could be expected to have a beneficial effect. Indeed, the prior art teaches that the results of a modification like walking a substituent around a ring were highly unpredictable.

Sohda II has only one pyridyl with a methyl substituent, compound 58. There is nothing in Sohda II from which one skilled in the art would conclude that a methyl in a different position on the pyridyl ring would improve efficacy or avoid or reduce compound 58's identified negative side effects.

Mosberg opines that the '200 Patent teaches that walking a substituent around the ring was a process "known" to Takeda. Many common (as well as sophisticated) chemical processes were no doubt known to Takeda; that is beside the point. The issue is whether there was any ground for a reasonable expectation of success that can be located in the prior art by a person of ordinary skill to choose a particular process to achieve the desired goal.

Mosberg gives three sets of examples[65] from the illus-

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[65] Mosberg discusses compounds 1 and 2; compounds 18 and 19; and compounds 31, 32 and 33 from the '200 Patent. In Sohda II,

trations in the '200 Patent that show either a methoxy (CH_3O) or a chloro (Cl) being "walked around" a different ring, a benzene ring.[66] He does not assert, however, that any of the disclosed results from that process taught that such a process would be likely to lead to any success, or that any particular position on a ring was likely to more efficacious or less toxic than any other. None of the three examples includes a substituent at the 5th position on the ring, where pioglitazone's substituent is located.

An examination of the efficacy data from Sohda II for the phenyl compounds to which Mosberg points suggests that substituents in a lower ring position may be more potent, principally by comparing the efficacy scores for substituents in the 4th position with those in the 2nd position.[67] Alphapharm has not shown, however, that one skilled in the art would have understood that these results were transferable from a phenyl to a pyridyl compound, that they would pertain to a comparison between a substituent in the 6th and 5th positions, or that they would eliminate toxicity.

Mosberg argues that Takeda's historical experience confirms his opinion that it was expected that one

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these are compounds 32 and 31; compounds 13 and 12, and compounds 5, 4, and 3, respectively.

[66] A benzene ring, in contrast to a pyridyl ring, does not have a nitrogen atom. A compound with a benzene ring is referred to as a phenyl.

[67] Alphapharm did not make this comparison or argument at trial.

would simply walk the methyl around the ring. This is, of course, an improper use of hindsight. Nonetheless, Takeda's historical experience is directly to the contrary. Compounds (c), (d) and (e) were each first synthesized in 1983; pioglitazone was first synthesized in 1982. Takeda clearly did not move from compound (b), which had been synthesized in 1978, to pioglitazone by "walking the ring."

Even if Takeda had moved away from compound (b) by "walking the ring," it would have discovered significant toxicity problems as soon as it synthesized and then tested each of the other methyl substituents on the 2-pyridyl ring. As illustrated in Table 1, compounds (d) and (e) each have significant toxicity. Compound (c) failed the chick lens assay screening. In sum, Alphapharm has not shown that one skilled in the art would have been motivated to move to pioglitazone by "walking the ring."

b) Homologation

Alphapharm has no more success with its argument that one skilled in the art would have been led to create a homolog of a methyl substituent on the 2-pyridyl ring,[68] than it did with its ring-walking argument. Alphapharm has failed to show that the prior art would have invested in a person with ordinary skill in the art a reasonable expectation that the substitution of an ethyl for an methyl would lead to beneficial results.

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[68] As noted earlier in this Opinion, a homolog is a chemical structure that differs from the parent compound by a single, constant increment of one carbon (and associated hydrogen atoms), such as adding a methyl group.

Sohda II describes over a score of compounds with a methyl substituent and eight compounds with an ethyl substituent. There is no discernable pattern of biological activity associated in a comparison of the two substituents in the prior art. Nothing in the prior art suggests that the process of substituting an ethyl for a methyl would be of any more assistance than using any other of the many possible substituents or changing course entirely and adopting a base structure other than the 2-pyridyl ring.

Indeed, Alphapharm has not identified any basis to find that even those with great skill understood in the 1980's (or even today) that the substitution of an ethyl group for a methyl group is likely to have a beneficial effect on biological processes. Our understanding of the biological properties of compounds is too rudimentary even today to allow us to form reasonable expectations regarding such a result.

In particular, Alphapharm is confronted again with the significant hurdle placed by the toxicity found in compound (b). Having found such high levels of toxicity to the heart, liver, and blood cells in compound (b), it has not pointed to anything in the prior art that would suggest that creating a homolog of the compound would be likely to reduce much less eliminate toxicity, either in any particular body system or as a whole.[69]

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[69] If one of ordinary skill in the art were confronted with toxicity issues, she would be "well-advised," according to Danishefsky, to try substituents that would change significantly the dipole moment of the molecule, that is the electron density of the compound. Examples of such substituents do not include an ethyl,

Ignoring entirely the substantial issue of compound (b)'s toxicity, Mosberg asserts that Sohda II teaches that the substitution of a methyl increases potency, and specifically that a comparison of Compounds 57 and 58 in Sohda II demonstrates that homologation increased the efficacy of pyridine compounds. Compound 57 is the unsubstituted pyridine ring; compound 58 is compound (b) (the 6-methyl on the pyridine ring).[70]

A more straightforward reading of Sohda II indicates that its authors understood that homologation does not ameliorate toxicity. The Sohda II authors point out that "[a]lthough compounds 56, 57, 58, 59 and 63 in Table IV showed potent activities, they, *especially 57 and 58,* caused considerable increases in body weight and brown fat weight." (Emphasis added.) One of ordinary skill in the art would therefore have been more likely to conclude from Sohda II that homologation had no tendency to decrease unwanted side effects and to focus research efforts elsewhere. There were other compounds described in Sohda II as efficacious as compound 58, including one with no identified side effects or toxicity. And, as already noted, the authors of Sohda II recommended investigation of three other compounds, not compound 58.

Mosberg argues that the '200 and '779 Patents teach

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and do include methoxies, alcohols, and halides, among many others.

[70] Compounds 57 and 58 were reported in Sohda II to have the same effect on hypoglycemic activity (a score of 3), while compound 57 scored 2 and compound 58 scored 4 with respect to plasma triglyceride-lowering activity.

that Takeda "may" prefer to use the lower alkyls[71] and in particular a methyl (CH_3) or an ethyl (C_2H_5) as substituents, and therefore it would not be surprising if Takeda used an ethyl substituent on a pyridyl ring. He relies on the Nohara Article and Sohda II as evidence that homologation was routine at Takeda. The test, of course, is not what Takeda might have tried, but whether one skilled in the art would have a reasonable expectation of success from synthesizing the homolog.

In any event, nothing in the '200 and the '779 Patents, or in any other publication from Takeda, would have given one skilled in the art an expectation of success from the substitution of an ethyl for a methyl. In its patents, Takeda specifically claims a variety of substituents on identified systems. For example, the '779 Patent includes substituents on a pyridyl or thiazolyl group, noting that "[a]s examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.) and hydroxyl."

Finally, Mosberg points to specific illustrations in the '200 Patent that demonstrate to him that Takeda was aware that the substitution of a methyl with an ethyl "should be carried out to test for useful compounds." Again, this is not an opinion that there was any reasonable basis for an expectation of success. In any event, when the specific illustrations selected by Mosberg are actually examined, using the efficacy data on those same compounds as provided by Sohda

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[71] Alkyls are linear chains of carbon atoms singly bonded to other carbon atoms or hydrogen atoms.

II,[72] it is immediately apparent that the prior art did not teach that the substitution of an ethyl for a methyl was likely to be beneficial. Sohda II shows a higher combined efficacy score for the methyl over the ethyl for one set, and an identical combined score for the methyl and the ethyl in the second set. The third set in the '200 Patent includes five compounds, but only three of the five are discussed in Sohda II. This set is a homologous series, with a CH_2 component repeatedly added. The Sohda II efficacy scores show no pattern, however, from the addition of the carbon atom.[73]

The position taken by Alphapharm's expert is perhaps best captured by his annotations to the expert report of Takeda's expert Danishefsky. On that report, he wrote in the margin that he agreed that a review of the biological effects of various substituents, as disclosed in the Sohda II article, made it clear that biological activity is "unpredictable." He added, "but this does not in [any]way make the choice of such analogs less obvious to try."[74] The test, of course, is

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[72] Mosberg cites to three sets of examples in the '200 Patent: compounds 3 and 4; compounds 5 through 9; and compounds 15 and 16. In Sohda II, these are compounds 36 and 37; 38 to 40 (only three of the five are reported in Sohda II); and 11 and 14.

[73] The compound in the middle of the series has the highest score.

[74] Additional annotations by Mosberg indicate that he did not believe that there was any reasonable expectation of success from any particular modification of the molecule. He agreed that "there is no data or information to even suggest that substitution of an ethyl for a methyl substituent would lead to predictable improvements in blood glucose or triglyceride lowering activity." Mosberg added in the margin, "there is no predictability only logical choice of analogs to try." As a final example, Mosberg notes in another annotation, that an effect on toxicity from

not whether it is "obvious to try" the synthesis of a particular compound, *see, e.g., In re O'Farrell,* 853 F.2d 894, 902 (Fed.Cir.1988), but whether one skilled in the art would have a reasonable expectation of success from doing so. At trial, the best the expert for Alphapharm could offer is that essentially anything can happen when one modifies a compound, so a change for the better might happen, and if it did, it would not be surprising. This does not come any closer to articulating a reasonable expectation of success.

In summation, Alphapharm's counsel tried with no success to limit the damage done by its expert's testimony. Admitting that there is inherent variability in the biological effects produced from even small changes in the structure of chemical compounds, he argued that a variation in the degree of an effect is entirely expected and is not surprising. He suggested that what would be surprising was to find an effect from the small change in the composition of a molecule in an entirely different body organ or system. Again, the issue is not whether something would be surprising, although the discovery that pioglitazone was non-toxic certainly qualifies as a surprising and unexpected event, but whether one could reasonably expect success.

In sum, even if compound (b) could have been identified by one skilled in the art as a lead compound worthy of further investigation, Alphapharm has failed to show that such a person would have had a reasonable expectation of success in synthesizing the pioglita-

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small structural changes "can be neither expected nor unexpected. It would *not* be surprising."

zone molecule. Alphapharm has not shown that pioglitazone was prime facie obvious.

D. Objective Indicia of Non-Obviousness

1) Unexpected Results

Given Alphapharm's failure to show prima facie obviousness, there is no need for an extended discussion of the objective factors used to evaluate obviousness. For reasons already described, pioglitazone's non-toxicity was entirely unexpected. Compound (b) was a highly toxic compound, and nothing in the prior art would have led one skilled in the art to expect that the 5-ethyl on a 2-pyridyl ring would be non-toxic. As Alphapharm's Rosenberg admitted at his deposition, pioglitazone is "clearly superior" to compound (b) because of its non-toxicity.

There is one evidentiary issue that arose in connection with the issue of unexpected results that requires some discussion. Alphapharm offered evidence at trial that a long-term study of the effect of pioglitazone in dogs, conducted by Upjohn after Takeda had applied for what became the '777 Patent, suggested that pioglitazone may lead to an increase in heart size, and thus has some toxicity. An Upjohn scientist who testified at trial discounted that interpretation of the test results. It is unnecessary to make any findings regarding this evidence, however, since it is entirely irrelevant to the issue of whether pioglitazone's non-toxicity, as disclosed in the '777 Patent, was an unexpected result.

Pioglitazone has, of course, been approved by the

FDA and the defendants challenge Takeda's patent because they believe it is an effective and non-toxic drug that will be profitable for them to sell. As significantly, while it may be appropriate to use later-acquired evidence to bolster a finding of unexpected results,[75] to illustrate for instance that an invention is even more beneficial to mankind than was originally understood, *see Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004), it is another thing altogether to suggest that after-acquired evidence should be used to undercut what appeared at the time of the patent application to be unexpected results. For instance, it would be entirely unfair to the patent applicant to discount what appeared at the time of an application to be unexpected results because our advancing and improved scientific knowledge allows us to understand why such results are to be expected. Therefore, as with all objective factors used to analyze the obviousness issue, after-acquired evidence of unexpected results should not be used to undermine a patent without a careful analysis of relevance. Here, the Upjohn tests, conducted long after the application for the '777 Patent, are irrelevant.

2) Additional Secondary Considerations

Evidence concerning other objective factors also shows that pioglitazone was a non-obvious invention. First of all, it is a huge commercial success. ACTOS® was launched in 1999, and by 2003 held 47% of the

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[75] There is, for example, strong evidence that the scientific community has come to understand that pioglitazone has a measurable and unexpected advantage over the other TZD on the U.S. market.

TZD market, as well as 9.9% of the total OAD market. In 2003, the gross sales of ACTOS® exceeded $1.7 billion. ACTOS® is the embodiment of pioglitazone, the invention disclosed in the '777 Patent, and therefore this commercial success can presumptively be attributed to the invention itself.

Pioglitazone also responds to a long felt but unmet need in the market of pharmaceutical treatments of diabetes. The introduction of TZDs, led by Rezulin® in 1997, revolutionized the care of diabetes. Rezulin®, however, has been removed from the U.S. market due to issues associated with liver toxicity, and today, only ACTOS® and Avandia® are available. Out of the millions of TZDs, only these two have been found to be safe and effective to treat insulin resistance in the muscle.

Alphapharm presents several arguments in a futile effort to undermine Takeda's compelling objective evidence of non-obviousness, particularly its evidence of commercial success. While Alphapharm concedes that there is evidence both of commercial success and that the successful product is claimed in the patent, it argues that other factors serve to undercut "the prima facie case of nexus" between the commercial success and the claimed invention.

Alphapharm argues that much of the commercial success of ACTOS® is due to events that were unforeseen at the time that the '777 Patent issued, such as the withdrawal of Rezulin® from the market, and an unexpected rise in obesity with an accompanying in-

crease in the incidence of diabetes.[76] These arguments miss the mark. There is no requirement that the invention be the only successful product in its market niche or the most successful. Moreover, ACTOS® would have been an important and successful invention by any reasonable measure even if the incidence of diabetes had remained unchanged since the time of the invention.

Alphapharm also argues that Takeda's success is more attributable to its marketing efforts, particularly its partnership with Eli Lilly, than the inherent value of the invention. This argument flies in the face of the strong evidence from medical practitioners about the benefits and the perceived benefits of ACTOS®. In any event, Takeda and GlaxoSmithKline invest roughly the same amount of money in their efforts to market their two TZD products, and both drugs have found success.

Finally, Alphapharm argues that Takeda's prior art patents, particularly the '200 and '605 Patents, undermine the nexus between ACTOS®' commercial success and the non-obviousness of the '777 Patent. The suggestion is that because Takeda had the right to exclude others from making the closest prior art compounds, the ability of other companies to enter the TZD market was stifled.[77] The argument is com-

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[76] There is no need to explore the extent to which the perceived rise in obesity and diabetes is due to a redefinition of obesity in 1998, and a change in the diagnostics for diabetes in 1997.

[77] In making this argument, Alphapharm relies on *Merck*, 395 F.3d at 1377, but in doing so, reads the case far too broadly. In *Merck* the patent at issue was a method claim for the use of a particular compound, which was protected by a patent owned by Merck. *Id.* at 1366. Because Merck owned the underlying pat-

pletely specious. Alphapharm has not shown that any of the compounds disclosed by Takeda in its patents were viable candidates for commercial development. Takeda's competitors had every opportunity to develop new compounds that were improvements over the compounds Takeda disclosed. This is exactly what Sankyo did in developing troglitazone, the active ingredient in Rezulin®. The patent that protects troglitazone lists the '605 and '902 Patents as prior art. The fact that only one other company has a TZD in the market today, despite the commercial opportunities available for an effective insulin sensitizer, is strong secondary evidence of pioglitazone's non-obviousness.

In sum, Alphapharm has not carried its burden of showing that the invention of pioglitazone was obvious. It has searched for a theory of obviousness, and its efforts have proven futile with each iteration of a theory.[78] Alphapharm's Section 355 Statement did not articulate a successful theory of obviousness, and its efforts to create one through the direct testimony of its expert, and yet another one as the trial unfolded all failed. Nothing in the prior art would have given one skilled in the art any reasonable expectation that the creation of pioglitazone would result in the discovery of an anti-diabetic treatment that was effica-

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ent, and thus could prevent others from commercially developing the method of use at issue, the court found that the "chain of inferences fails on these facts." *Id.* at 1377. The case does not establish that commercial success is not probative simply because a patent holder also holds a prior art patent.

[78] It is telling that two of the defendants never sought to attack the '777 Patent on the ground that it was obvious, and a third defendant abandoned the theory of obviousness it had articulated in its own Section 355 Statement.

cious and non-toxic.

II. Inequitable Conduct

Mylan contends that the '777 Patent is invalid because Takeda engaged in inequitable conduct. Applicants for patents are bound by a duty of "candor and good faith" to the PTO. *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 04-1189, 04-1347, 04-1357, 2006 WL 231480, at *4 (Fed.Cir. Feb.1, 2006).[79] Included in the

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[79] The conduct of applicants while applying for patents is governed by 37 C.F.R. § 1.56 ("Rule 56"), which is promulgated by the PTO pursuant to 35 U.S.C. §§ 6 and 131. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1179 n. 8 (Fed.Cir.1995). The governing standard for evaluating defendant Mylan's claims of inequitable conduct is the regulation as it stood in 1986, when Takeda pursued its application for the invention covered by the '777 Patent. Seeid. In 1986, the regulation read in relevant part:

(a) A duty of candor and good faith toward the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to the examination of the application. Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. The duty is commensurate with the degree of involvement in the preparation or prosecution of the application.

(d) No patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence. The claims in an application shall be rejected if upon examination pursuant to 35 U.S.C. 131 and 132[sic], it is estab-

duty is the obligation of applicants to disclose information of which they are aware that is "material to the examination of the application." 37 C.F.R. § 1.56(a) (1985). The duty encompasses an "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information." *Purdue Pharma,* 2006 WL 231480, at *4, 438 F.3d at 1128.Materiality and intent "must be shown by clear and convincing evidence." *Id.* The burden of proof required to prove inequitable conduct has been described as a "heavy burden". *Hoffmann-La Roche, Inc. v. Promega Corporation,* 323 F.3d 1354, 1359 (Fed.Cir.2003)

For patents prosecuted before 1992, "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application as a patent." 37 C.F.R. § 1.56(a); *see Dayco Products, Inc. v. Total Containment, Inc.,* 329 F.3d 1358, 1365 (Fed.Cir.2003). Materiality is not limited to matters reflected in the claims of the patent, *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.,* 225 F.3d 1315, 1322 (Fed.Cir.2000), but embraces "any information that a reasonable examiner would substantially likely [sic] consider important in deciding whether to allow an application to issue as a patent." *Dayco Products,* 329 F.3d at 1368 (citation omitted);

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lished by clear and convincing evidence (1) that any fraud was practiced or attempted on the Office in connection with the application, or in connection with any previous application upon which the application relies, or (2) that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the application, or in connection with any previous application upon which the application relies.
37 C.F.R. § 1.56(a), (d) (1985) (emphasis supplied).

see Akron Polymer Container Corp. v. Exxel Container, Inc., 148 F.3d 1380, 1382 (Fed.Cir.1998). The standard for materiality is not a "but for" standard. *Merck & Co. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1421 (Fed.Cir.1989); *see also Digital Control Inc. v. Charles Mach. Works*, 05-1128, 2006 WL 288075, at *7 (Fed.Cir. Feb.8, 2006). It is not necessary to find that an examiner relied on the misrepresentation or omission at issue, only that it would have been "within a reasonable examiner's realm of consideration." *Hoffmann-La Roche, Inc.*, 323 F.3d at 1368 (citing *Merck & Co.*, 873 F.2d at 1421). Affidavits submitted to the PTO may be "inherently material." *Digital Control*, 2006 WL 288075, at *8, 437 F.3d at 1318; *see also, Refac Intern., Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 1583 (Fed.Cir.1996).

[16] Direct evidence of intent to deceive is "rarely available", but intent "may be inferred from clear and convincing evidence of the surrounding circumstances." *Purdue Pharma*, 2006 WL 231480, at *9, 438 F.3d at 1134 (citation omitted); *see also Ferring B.V. v. Barr Labs., Inc.*, 05-1284, 2006 WL 335601, at *8 (Fed.Cir. Feb.15, 2006). While a "court must weigh all evidence, including evidence of good faith" in determining intent, "a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." *Purdue Pharma*, 2006 WL 231480, at *9, 438 F.3d at 1134 (citation omitted).

If the duty is breached in a way that is both material and intentional, then the patent will be invalidated if

"the equities warrant a conclusion that inequitable conduct occurred." *Id.* at *4, 438 F.3d at 1128.The material misrepresentations or omissions must be "sufficiently serious in light of the evidence of intent to deceive, under all the circumstances, to warrant the severe sanction of holding the patent unenforceable." *Hoffmann-La Roche,* 323 F.3d at 1372.

Mylan has failed to carry its heavy burden of showing that Takeda engaged in inequitable conduct. Mylan principally claims that Takeda intentionally made material misrepresentations in its presentation of the comparative test results for the six compounds listed in Table 1 of the '777 Patent, and that Takeda should have added information concerning a seventh compound to the table.

There are many indicia of Takeda's good faith in its application to the PTO in 1986. First, with the exception of two test results it obtained in response to the Office Action, the test results Takeda presented to the PTO in Table 1 were drawn from reports that Takeda and its research partner Upjohn had used in 1984 to select five compounds, including pioglitazone, for further research and potential development as a pharmaceutical. Takeda had every incentive to reflect in those reports its best judgment about what the test results showed so that the companies' money and the scientists' energies would be spent as productively as possible. There is simply no basis to find that there was any misrepresentation in the 1984 reports, much less any incentive to misrepresent test data.

Second, Takeda identified the relevant prior art to the PTO. Both Sohda II and the '200 Patent were de-

scribed. In addition, the chemical structure for the closest prior art-compound (b) on Table 1, which is compound 58 in Sohda II-is set out in a diagram so that it can be easily compared to the chemical structure for pioglitazone and the other compounds listed in Table 1.

Third, Takeda did not manipulate the data presented in Table 1 to make pioglitazone appear better than its internal data reflected. For example, Table 1 shows that compound (b) is superior to pioglitazone in the reduction of both blood glucose and triglycerides. Even when the Office Action required Takeda to fill in three more data points in Table 1-the triglyceride data for rats for compounds (c), (d) and (e)-Takeda gave the PTO figures that were comparable to or superior to the figures for pioglitazone in Table 1.[80]

Fourth, Takeda had powerful additional evidence of the superiority of pioglitazone over the prior art which it did not present to the PTO. Report A-15-34 reflects the results of the in vitro chick lens assay [81] for many compounds, including those in Table 1. Only pioglitazone and compound (e) of the six compounds listed in Table 1 showed no evidence of toxicity in this test. This was additional evidence of the superiority of pioglitazone over the compound in the prior art to which it was most structurally similar, compound (b), which Takeda had at hand to share with the PTO if necessary.

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[80] Pioglitazone ED^{25} value for lowering rat triglyceride levels was shown as 3; the comparable values for compounds (c), (d) and (e) were reported as 6, 4 and 2, respectively.

[81] It was this test which had resulted in the abandonment of ciglitazone as a marketable pharmaceutical.

Fifth, there is no dispute about the superiority of pioglitazone over compound (b), the only prior art compound in Table 1. Mylan cannot explain how Takeda could have anticipated in 1984, when it created Reports A-15-13 and A-15-34, that information about compounds (c), (d) or (e) would be included in the PTO application or what additional explanations the examiner would seek in an Office Action.

Ignoring this powerful evidence that Takeda acted in good faith in its presentation to the PTO, Mylan has cobbled together a series of arguments in an effort to show inequitable conduct. As noted, its arguments relate to the presentation of data in Table 1. It emphasizes data concerning two compounds: compound (c), which is the 5-methyl homolog of pioglitazone, and compound 3894, which is the unsubstituted pyridyl ring. With respect to compound (c), Mylan contends that Takeda misrepresented the data regarding compound (c)'s potency to make it appear weaker than pioglitazone. It points out that compound (c) had no toxicity indicated on Table 1, and therefore, pioglitazone would not have appeared superior to compound (c) if their efficacy numbers were presented as comparable.[82] With respect to compound 3894, Mylan argues that Takeda had a duty to report the comparative test results for this compound on Table 1, but did not. Compound 3894 had comparable if not better efficacy than pioglitazone, but was rejected for development by Takeda due to its toxicity to the heart. In addition, as described below, Mylan raises a few other issues to attack Taeda's honesty in

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[82] Compound (c) failed the chick lens assay test, but those data were not presented to the PTO.

its presentation of Table 1 data.

Before addressing Mylan's categories of alleged misrepresentations, a few observations are in order. Many of Mylan's examples of the misrepresentation or omission of data rest on testing data it culled from surviving Takeda notebooks that were produced in discovery in 2004 and 2005. The screening tests were conducted approximately 20 years earlier, and not all of Takeda's laboratory notebooks have survived. Thus, Mylan's analysis rests on the fallacy that it has a complete set of the testing data from which to judge the completeness and fairness of the presentation of the testing results to the PTO.

There is a second flaw in Mylan's contention that Takeda should have used the experimental data lifted directly from the notebooks rather than the data in the reports on which Takeda and Upjohn relied to make their research decisions. Presenting raw, unanalyzed data from notebooks would have been both incomprehensible to an examiner and misleading. Indeed, the notebooks contain some test results for pioglitazone that are more favorable than those listed on Table 1 and test results for some of the other compounds that are less favorable than the descriptions of those compounds on Table 1.

Fujita analyzed all of the test results in 1984, and chose to include in Report A-15-34 those that he considered the most reliable. Takeda and Upjohn relied upon the data in that report in making critical business decisions, and it was entirely appropriate for Takeda to rely on that same data in preparing Table 1 for the PTO.

With two exceptions, which are discussed below and concern the strain and age of rats, Mylan has failed to show that there was any misrepresentation or material omission in Takeda's presentation of data. With respect to the two errors, Mylan has failed to show that the errors were either material or the result of any intentional misconduct by Takeda.

A discussion of Mylan's specific contentions follows. Its contentions are organized according to the column in Table 1 to which they relate. Its arguments concerning compound 3894-the compound not included on Table 1-are addressed last.

A. Misrepresentations

1) Mouse ED^{25} values

Mylan argues that most of the ED^{25} values for the lowering of blood glucose and plasma triglycerides in mice that were reported in Table 1 were false and misleading, and that the actual test results obtained by Takeda were not reported to the PTO. In particular, Mylan stresses data obtained in a single 1983 experiment in which pioglitazone and compound (c) were tested together or head to head,[83] and shown to have roughly the same ED^{25} values, while Table 1 reflects pioglitazone significantly outperforming com-

[83] Mylan makes a similar argument for compound (e), claiming that data from a single experiment in a Takeda notebook shows that compound (e) outperformed pioglitazone. For the reasons discussed in the analysis of the argument concerning compound (c), Mylan has not shown that a misrepresentation occurred in the presentation of the ED^{25} mice data on Table 1.

pound (c) in these measures.[84]

As already noted, the ED^{25} mouse data in Table 1 is identical to that contained in Report A-15-34. Mylan's assertion that there was a misrepresentation is based exclusively on the results of a handful of experiments Mylan located in surviving Takeda notebooks. There were many more experiments conducted by Takeda than are reflected in the surviving notebooks. Indeed, as has been explained previously, because there were so many screening tests performed, for many compounds Report A-15-34 presents a range of test results for the efficacy testing. It first lists the figure which Fujita selected as the most reliable, and then in parentheticals gives a range of test results.[85]

It was entirely appropriate, and indeed necessary, for Fujita to apply his professional judgment to the mass of test results and select the test results on which he felt that Takeda and Upjohn could best rely in the Fall of 1984. Not all tests yield similarly reliable data. Some of the test results from the Takeda notebooks on which Mylan has relied are preliminary two

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[84] Table 1 showed ED^{25} blood glucose and triglyceride lowering scores of 6 and 6 for pioglitazone, but 20 and 20 for compound (c). In the single experiment to which Mylan points, the comparable pioglitazone values were 5.2 and 14, but 6.4 and 18 for compound (c).

[85] For instance, the ED^{25} blood glucose data for compound (c) were reflected in Report A-15-34 as: "20 (2-5)". The data in the parenthetical represent the relative potency of compound (c) to ciglitazone, ciglitazone being accorded a rating of one. Fujita chose the test reflecting an ED^{25} value of 20 as the most reliable test, but by including the data in the parenthetical, reflected that the test results ranged from values between 8 and 20. Ciglitazone had an ED^{25} value of 40 in Report A-15-34.

dose tests, which would not yield reliable ED^{25} data. In other tests it appears that the effective dose is beyond the administered doses, and again would not be a reliable basis for determining the effective dose. In other surviving tests, where there does not appear to be any particular defect in the test, Mylan still has not shown that those data should have been used in Table 1 instead of the data Takeda chose to present there.[86] Without having all of the underlying test results from which Fujita selected the most reliable tests to calculate the ED^{25} values contained in Report A-15-34, it is simply impossible today to reconstruct why any single test was or was not chosen as the most reliable. What can be established today with confidence, however, is that Fujita had every motive to use his best judgment in 1984 in compiling the data for Report A-15-34, and it was those data which were presented to the PTO in 1986.

In this connection it is important to note that Takeda had given over fifty compounds to Upjohn, as well as KKA^y mice, so that Upjohn could replicate the efficacy testing that Takeda was doing in its own laboratories. Two scientists who were deeply involved in the 1984 diabetes drug program at Upjohn testified at trial and confirmed that Upjohn not only did its own efficacy testing but also that all of the results it ob-

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[86] Using the notebook data to create ED^{25} values, and after eliminating tests where only two doses were administered or where the dose response curve was flat (indicating that the ED^{25} value was beyond the range of doses tested), the data currently available results in an identical ranking of pioglitazone, and compounds (a) and (c) to that presented to the PTO: pioglitazone was superior to compound (c); compound (a) had the poorest performance. There was insufficient surviving data for the other compounds to do a meaningful comparison.

tained were consistent with the results that Takeda reported. These two scientists, neither of whom has any stake in this litigation, spoke highly of the competence and integrity of the Takeda scientists and its testing program. The existence of Upjohn's parallel testing program is yet another reason to find that Fujita used his best judgment in choosing the efficacy numbers (and other data) for Report A-15-34. Upjohn's scientists were in a position to disagree with his presentation of the data, and Fujita knew that.[87]

There are two additional arguments that Mylan makes about the presentation of the efficacy scores in Table 1 for mice. It points to comparisons with ciglitazone that were contained in monthly internal reports at Takeda in early 1984, and Report A-15-13, circulated in February 1984. These comparisons listed compounds that screening tests had determined were "five times as potent as ciglitazone." Pioglitazone and compound (c) were among the compounds found as having such a superior performance. Mylan argues that it is inconsistent to identify compound (c) as five times more potent than ciglitazone in these internal documents, and yet to list it on Ta-

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[87] In a chapter of a book published in 1990, the Upjohn scientists who testified at trial described research into ciglitazone, pioglitazone and other TZDs. They reported that Takeda discovered through its research that replacing the left hand moiety of ciglitazone with a 2-pyridinylethoxy produced compounds "approximately 5-10 times more potent than ciglitazone". They added that further testing of the compounds for efficacy and safety resulted in the selection of pioglitazone for development. Despite Mylan's arguments to the contrary, nothing in this general description of the Takeda screening program undermines the reliability of Report A-15-34, a report on which these same Upjohn scientists relied to make research decisions.

ble 1 as only two times as potent.[88]

Takeda's early screening tests were part of a program to find more potent and less toxic compounds than ciglitazone. They created new compounds, including compounds (c), (d) and (e) in mid-1983, and subjected them initially to two-dose tests, and those that survived that screening, to three-dose tests. During 1984, Takeda continued to test compounds. For the reasons already explained, there is no reason to doubt that Takeda used its best judgment in selecting the most reliable potency values for Report A-15-34 from among the universe of available test results,[89] and those same numbers appear in Table 1. Mylan has not shown that Takeda engaged in inequitable conduct by failing to give the PTO data reflecting the best performance by a compound, instead of the performance judged by extremely well qualified scientists as the most reliable performance.[90]

Finally, Mylan finds in another section of Report A-15-34 support for its argument that Table 1 was mis-

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[88] On Table 1, ciglitazone's ED^{25} values for lowering blood glucose and triglyceride levels in mice are both 40, while compound (c)'s are listed as 20.

[89] As already noted, Report A-15-34 did include a range of potency, comparing each compound's potency to ciglitazone, and compound (c)'s range of potency was listed in Report A-15-34 as "2-5" or two to five times as potent as ciglitazone.

[90] Mylan has argued that Takeda should have given the PTO the range of test results reflected in the parentheticals in Report A-15-34. Mylan has not shown that the range of results would have been material to the examiner or anything other than an additional layer of detail that was unnecessary for the examiner to perform his function. Giving the PTO the most reliable test data, as opposed to a summary of all test results was sufficient to meet Takeda's obligations to the PTO.

leading. In Figures 5 and 6 of Report A-15-34, pioglitazone is shown as somewhat more potent in mice, and as creating less "brown fat" in rats, than compound (c).[91] Pioglitazone is not shown in these figures, as it is in Table 1 of Report A-15-34 (and in Table 1 of the patent), as over three times more potent than compound (c). Takeda apparently chose to use some of the test results for compound (c) in these figures that were different from the values it chose as the most reliable when it created Table 1 of Report A-15-34.

Mylan has not shown that Takeda should have presented the data used to create the two figures in Report A-15-34 instead of the Table 1 data to the PTO. The two figures do not even have numbers associated with a particular compound; the figures are simply graphs composed of points entered on a logarithmic scale. One can only estimate, and very roughly at that, what the underlying values are. The only reliable *numbers* in Report A-15-34 are those that were reported to the PTO.

Takeda's testing, which was extensive, was nonetheless preliminary, screening testing, used to identify a small group of compounds, ultimately five, for more intensive testing and potential development. Takeda was under no obligation to conduct more extensive testing before applying for a patent; its only obligation was to present its results as of that time honestly. Mylan has not shown that Takeda violated that

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[91] Takeda created a graph of the data using these two parameters and from that graph formed the hypothesis that the increase in the brown adipose tissue ("brown fat") in the rats may be partially due to the pharmacological potency of a compound.

obligation in connection with the mouse efficacy data.

2) Rat ED^{25} values

Mylan argues that some of the ED^{25} values for plasma triglyceride lowering that Takeda obtained from testing rats were not obtained in the manner Takeda described to the PTO in the '777 Patent application and the Amendment, and that Takeda concealed some of the results it did obtain from its testing.[92] Mylan makes three separate arguments, but has not shown in connection with any of them that Takeda engaged in inequitable conduct.

a) ED^{25} value for pioglitazone

Relying again on surviving notebook data, Mylan argues that Takeda misrepresented the ED^{25} in rats for pioglitazone. Table 1 reported the value as 3 for pioglitazone, but Mylan points to data from tests reflected in surviving notebooks that show different values, one of them lower than a 3.[93] For the reasons already discussed, Mylan has not shown that there was any misrepresentation by Takeda. Takeda took the figure for pioglitazone from Report A-15-34, and that was a reliable source of data to present to the PTO.

b) Exclusion of a control animal

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[92] In its summation, Mylan only mentioned one of these three issues: the failure to tell the PTO that a control animal had been excluded from an experiment.

[93] The ED^{25} values identified by Mylan for pioglitazone are 17.9, 7.8 and 2.3.

Mylan argues that Takeda misrepresented its testing protocol to the PTO when it indicated that there were five rats in each testing group, including the group of animals used as a control. Mylan argues that Takeda should have advised the PTO that in one test it had omitted test data obtained from one control animal.[94]

In responding to the Office Action, Takeda conducted experiments to obtain ED^{25} values for plasma triglyceride lowering in rats for compounds (c), (d) and (e). One of the five animals in the control group gained comparatively little weight during the test period and had anomalous readings for other pertinent characteristics.[95] In averaging the data obtained from the control group in this test, a Takeda researcher chose to eliminate the readings from this one animal.

The "censoring" of animals in biological testing is encouraged where results are not representative and where inclusion would be misleading. The exclusion of one control animal was entirely appropriate here and reflects the exercise of sound scientific judgment. Scientific publications do not always report the exclusion of one laboratory animal in their description of test results, and there is no basis to find that it should have been reported to the PTO or that the test results should have included the readings obtained from this single animal.

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[94] Mylan initially argued that Takeda should not have eliminated the control animal from its calculations since the censoring of the animal dramatically altered the test results. It appears to have abandoned this argument. As explained above, the censoring was entirely appropriate.

[95] The control animal had an elevated NEFA level (non-esterified fatty acids), which indicated that it was either not sufficiently eating or assimilating its food.

Mylan also argues that Takeda's statement in the Amendment about control group values was misleading because it did not explain that an animal had been censored in one experiment. In the Office Action, the examiner expressed uncertainty about how to interpret the Table 1 data, noting *inter alia* that the disclosure failed to provide "values for the control group." In response, Takeda explained that

> Each control value of blood glucose and TG is determined to be 100% and that of "liver weight", "heart weight" and "number of erythrocyte" is estimated to be zero % from the above numerical expressions. Therefore it is *meaningless to show the values of the control.* The disclosure of the table ... is sufficient for those skilled in the art to interpret the data.

(Emphasis supplied).

Takeda's response to the examiner's inquiry was entirely accurate. It explained why one skilled in the art would understand all control values to be 100%, and the performance of a compound to be measured against that assumed control value. This explanation helped the examiner to read Table 1; it did not concern the particular experiment in which an animal was censored or even the circumstances more generally in which one animal would be censored in order to obtain a reliable test result. Mylan has not shown that there was any misrepresentation or material omission.

c) ED^{25} data for compound (d)

As noted, the Office Action requested that Takeda provide triglyceride effectiveness data for compounds (c), (d), and (e). These were the only three fields of data not completed in Table 1 as it was originally presented to the PTO. When the supplemental testing done to respond to the Office Action demonstrated no triglyceride-lowering activity in compound (d), Fujita lifted the results from Report A-15-34 and reported a "4" as the ED^{25} value, a number close to the value of "3" reported for pioglitazone. Ciglitazone's value was "70".

Mylan has not shown that there was any effort to mislead the PTO by reporting a "4" for compound (d). If Takeda had reported that compound (d) had no potency, rather than fairly strong potency, then Mylan may have had grounds to complain. As it was, what Takeda did was utterly inconsistent with any effort to place pioglitazone in a more favorable light than it deserved.

3) Toxicity in Rats

Mylan has argued that Takeda misled the PTO by falsely describing the strain and age of rats that it used to obtain toxicity data.[96] It has failed to show inequitable conduct in either instance.

a) Strains of rats

The studies measuring the potency of compounds

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[96] It is not entirely clear if Mylan continues to press these arguments. Mylan did not mention either of these issues in its summation.

were performed in Sprague-Dawley rats, while the toxicology tests were performed in Wistar rats. Takeda represented to the PTO that all of the testing had been performed in Sprague-Dawley rats.[97] Mylan has not shown that this error was material.

Two of the most common strains[98] of laboratory rat used in toxicology studies are Wistar and Sprague-Dawley. Both strains are of healthy animals, and toxicology assays are almost always performed in healthy animals in order to rule out other causes of abnormalities.[99] The Sprague-Dawley strain originated from crosses with Wistar females and remains genetically similar to the Wistar today. Indeed, there are still no genetic markers to differentiate the two strains. Credible expert testimony established at trial that the use of Wistar rats instead of Sprague-Dawley rats did not change the reliability of the conclusions that were presented to the PTO since the

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[97] The '777 Patent described the experimental process for obtaining data regarding lipid lowering activity and toxicity in rats. The patent represented that the former tests had been conducted with "[m]ale Sprague-Dawley rats" and the latter with "[m]ale and female Sprague-Dawley rats."

[98] A strain is a group of individuals who share a presumed common ancestry and have clear-cut physiological, but not usually morphological, distinctions. Wistar and Sprague-Dawley rats are both outbred strains, meaning that they are maintained as colonies of animals of unidentified genotype. Individual animals from an outbred stock may differ markedly in their genetic characteristics. In contrast, due to cross-breeding of brother-sister pairs in inbred strains over many generations, individuals within an inbred strain are treated as genetic clones.

[99] Three dose effectiveness tests were done in normal Sprague-Dawley rats to obtain plasma triglyceride levels. If the levels of treated animals were reduced, that was an indicator of the compound's antidiabetic activity.

same strain was used across the toxicology experiments.[100] There is simply no basis to find that the error was material or made as a result of an intent to mislead.

b) Safety margin analysis

Mylan argues that the value of the safety margin analysis that Takeda developed in response to the Office Action is undercut by the fact that Takeda used Sprague-Dawley rats for its efficacy data, but Wistar rats for the toxicity testing. This argument reflects a fundamental misunderstanding of the testing process. Since the same strain of rat was used as both the control animal and the animal receiving the compound in any given experiment, the efficacy data and the toxicity data were each derived from a scientifically sound experiment. Scientists commonly derive safety margin data using two different animal models. Again, Mylan has not shown that there was any failure to provide the PTO with information material to the examiner.

c) Age of rats

The '777 Patent and the Declaration both explain that the toxicity studies in rats were two-week tests done in rats that were "5 weeks old". In one of the two-week toxicology studies, however, the one in which pioglitazone itself was tested, at the initiation

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[100] For example, when two-week toxicity studies were done in both Wistar and Sprague-Dawley rats for pioglitazone, the results were essentially equivalent.

of the study the rats were six weeks of age.[101] Since the results were based on normalized weight calculations and a comparison to control groups of the same age as the test groups, the error in describing the age of the rats was immaterial.

Mylan argued at trial that testing pioglitazone in animals that are one week older gave it an advantage because rats at that age are going through puberty and as more mature and bigger animals will be less susceptible to the toxic effects of the compounds. The credible scientific evidence at trial established that this small difference in age at the point in which the tests began had no effect on the validity of the test results.[102]

Puberty is a process and individual rats generally enter this process at any time between thirty-five to sixty days, that is, between five to eight and a half weeks. Tests conducted on rats that are from five to seven weeks old and from six to eight weeks old are thus each conducted on rats presumptively undergoing puberty. Using control animals of the same age and normalizing organ weights to body weight, which Takeda did for each test, are sufficient to eliminate any variations of significance among the tests.

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[101] Pioglitazone and compound 3894 were tested in rats at least six weeks old. The compounds listed on Table 1 other than pioglitazone were tested in rats five weeks old.

[102] Even though Alphapharm purported to be pursuing an obviousness claim, it chose to cross-examine Takeda's expert on the issue of the age of the rats, using a series of graphs it prepared based on data drawn from Takeda's test results. Correctly interpreted, the graphs in fact underscored the expert's opinion that the one week age difference had no impact whatsoever on the test results.

B. Omission: Compound 3894

Mylan argues that Takeda had an obligation to disclose to the PTO activity and toxicity data regarding compound 3894, a compound revealed in the prior art, specifically in Sohda II. Compound 3894 is a TZD molecule with a 2-pyridyl ring at the left end, but no substituents on that ring. It is the parent structure for the left hand moiety of the pioglitazone molecule. Mylan argues that if Takeda had revealed that compound 3894 had a comparable activity and toxicity performance to pioglitazone then the PTO "may" have concluded that pioglitazone was not patentable over prior art. Put another way, Mylan argues that Takeda falsely asserted to the PTO that the introduction of an ethyl group to the 2-pyridyl ring produced unexpected results because it knew that pioglitazone is not superior to compound 3894.

In the '777 Patent Takeda made the following statement:

> As is apparent from the experimental results given in Table 1, Compound (I) of this invention is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with the compounds (a), (b), (d) and (e). *Such an effect as above caused by the introduction of an ethyl group is quite unexpected.*
>
> (Emphasis supplied.)

Compound 3894 is toxic. As reflected in Reports A-15-13 and A-15-34, two-week toxicity tests performed in rats demonstrated a statistically significant toxicity to the heart known as cardiomeglia or enlargement of the heart. Mylan has not shown either that Takeda should not have relied on the results reflected in Report A-15-34 in making judgments about the unexpected results achieved through the introduction of an ethyl group, or that the underlying test results on the toxicity of compound 3894 were unreliable.[103]

Mylan points to Takeda documents in which the effects on the heart by compound 3894 were described as "weak" or "mild", as well as Report A-15-13 from February 2004, where this compound was described as one of four compounds that appeared less toxic than the others that had been tested as of that time, and which because of their potency, appeared "much easier to continue further studies including clinical trials." These preliminary views are insufficient to overcome the compelling evidence that as of the Fall 2004, when Report A-15-34 was prepared and Takeda and Upjohn made their judgments about what toxicity levels would be disqualifying and which compounds warranted further testing, compound 3894 was disqualified because of its toxicity.

As already discussed in connection with the discus-

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[103] Mylan first suggested that the statistical significance of the toxicity finding needed to be confirmed through an analysis of variance or ANOVA, with a Dunnett's post-test. Mylan, however, did not perform that test, and when Takeda's expert did, the testing confirmed Takeda's finding of statistical significance. Mylan's expert then speculated that the testing results might be an "artifact". He suggested that the results be confirmed through retesting, but Mylan undertook no such testing.

sion of the issue of obviousness, the closest prior art to pioglitazone was compound (b), not compound 3894.[104] Moreover, it was important to compare pioglitazone to ciglitazone, which had advanced as far as human trials before it had to be abandoned because of toxicity. It was unnecessary for Takeda to present testing data for compound 3894 as well. By presenting the comparison with compound (c), Takeda was presenting data with its methyl-substituted homolog, which was more closely related to pioglitazone in its chemical structure than the unsubstituted compound 3894.

C. Intent

It is undisputed that Takeda made two misstatements of fact to the PTO. Takeda erred in describing the strain and age of rats used in the toxicity testing.

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[104] By the time of its summation, Mylan had abandoned any claim that compound 3894 was the closest prior art. It argued that In re Johnson, 747 F.2d 1456 (Fed.Cir.1984), requires an applicant for a patent to present information about any relevant prior art, even if it is not the closest prior art. Johnson reaffirms that an applicant must compare the invention to the closest prior art. Id. at 1461. That was done here. Johnson also addresses the duty of comparison where there are two equally close references. Id. That is not an issue presented here.

One Mylan expert had asserted without any analysis that compound 3894 was the closest prior art, but admitted on cross examination to each of the facts on which Takeda's far more impressive and careful expert relied in forming his conclusion that a substituted pyridyl, such as compound (b), is closer structurally to pioglitazone than an unsubstituted pyridyl. To give but one example, the introduction of an alykyl substituent changes the shape of the TZD molecule dramatically, which can have profound effects on the interface between the TZD and the PPAR-gamma molecules.

Neither of these errors was material. Mylan has failed to show that Takeda made any other misstatements or failed to provide the PTO with material information. In any event, Mylan has utterly failed to show that Takeda ever acted in bad faith in the prosecution of the '777 Patent.

The evidence of Takeda's good faith is abundant. Takeda's lead scientist for this project was Fujita. As the Chief Scientist of the Biology Research Laboratory, he had ultimate responsibility for the conduct of the screening tests run in 1983 and 1984; he chose the efficacy values for Report A-15-34; and he recommended pioglitazone as one of the twelve compounds from which Takeda and Upjohn should select their candidates in October 1984 for more intensive studies and possible development as a pharmaceutical. He did not include either compound 3894 or any other Table 1 compound among that group of twelve. Fujita has long since retired from Takeda, but he testified at trial. He was an entirely credible witness. Despite extensive cross-examination, he remained a patient, careful witness who worked hard to give precise, accurate answers to every question that he was asked. Although he had no current recollection of many of the details of events from the mid-1980s, his testimony established beyond peradventure that he had used his best scientific judgment and considerable expertise at that time. He is, in short, an honorable man and distinguished scientist. There is absolutely no evidence that he ever acted with intent to deceive either other scientists at Takeda or Upjohn in preparing Report A-15-34 or the PTO.

Fundamentally, Mylan has never been able to over-

come the hurdle presented by the fact that Takeda's work was undertaken in collaboration with Upjohn, and that the Table 1 data were taken directly from Report A-15-34. Even if his character would have permitted him to act other than with complete scientific integrity, Fujita had no *motive* to use anything other than his best judgment in creating Report A-15-34. He had no way to know what results Upjohn had obtained in testing these same compounds and whether its judgments would agree with his own, and he certainly had no ability to anticipate what data might be important in any future PTO proceedings. As significantly, he had no motive to fabricate data for compounds such as compound (c) that were not even in the prior art.[105] Fujita's only identifiable motive was to choose as wisely as he could the most promising compounds into which Takeda and Upjohn would invest significant resources to determine if they had successfully identified an efficacious, safe compound for use as a pharmaceutical. To place Mylan's argument in stark relief, Mylan would have vehemently complained if Takeda had presented to the PTO any toxicity or efficacy numbers other than those in Reports A-15-13 and A-15-34.

Many of the arguments pressed by Mylan (and Alphapharm) at trial flow from a convoluted theory of a conspiracy by Takeda to obtain patent protection for

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[105] If, for instance, compound (c) had been a better choice for pharmaceutical development than pioglitazone, then Takeda would have had no reason not to select compound (c) for development. It certainly would have been able to show the PTO its unexpected superiority over prior art compound (b) easily, given compound (b)'s extreme toxicity.

the 6-ethyl.[106] The 6-ethyl is a homolog of compound (b), which is a prior art compound. This theory suffers from several flaws, including most prominently the fact that when Fujita's department applied internally within Takeda to begin the process of applying for the patent that became the '777 Patent, it sought patent protection for the pioglitazone molecule alone and no other compound. In addition, of course, Takeda has never developed a 6-ethyl compound.

In sum, Mylan has failed to carry its burden of showing either a material misstatement or omission. It has also failed to present any evidence of intent to deceive the PTO.

Conclusion

Each defendant having failed to carry its burden at trial, the challenges to the '777 Patent by Alphapharm on the ground of obviousness and by Mylan on the ground of inequitable conduct are denied. Takeda shall submit a proposed judgment.

SO ORDERED.

S.D.N.Y.,2006.
Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.
417 F.Supp.2d 341

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[106] The '777 Patent claims include not just the pioglitazone molecule, but also each of the ethyls on the 2-pyridine moiety. The ethyl in the sixth position is referred to as the 6-ethyl.

Not Reported in F.Supp.2d, 2005 WL 2092920
(S.D.N.Y.)

United States District Court,
S.D. New York.
TAKEDA CHEMICAL INDUSTRIES, LTD. and
Takeda Pharmaceuticals, North America, Inc.,
Plaintiffs,
v.
MYLAN LABORATORIES, INC. and UDL
Laboratories, Inc., Defendants.
No. 03 Civ.8253 DLC.
Aug. 31, 2005.

David G. Conlin, Barbara L. Moore, Edwards & Angell, LLP, Boston, MA, for Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda").

Martin B. Pavane, Mindy H. Chettih, James P. Doyle, Cohen, Pontani, Lieberman, & Pavane, New York, New York, for Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively "Mylan").

OPINION AND ORDER
COTE, J.

On July 7, 2005, Mylan moved for reconsideration, pursuant to Local Civil Rule 6.3, of this Court's June 21, 2005 Memorandum Opinion and Order ("June 21 Order") precluding Mylan from offering at trial any evidence as to the invalidity of U.S. Patent No. 4,687,777 (the " '777 Patent") except that based on a

theory of obviousness as set forth in its September 8, 2003 Notice of Paragraph IV certification to Takeda. Mylan has abandoned the theory of obviousness identified in its Pargraph IV certification and after the close of fact discovery has sought to substitute a new theory. For the reasons stated herein, Mylan's motion for reconsideration is denied.

Background

On September 8, 2003, Mylan sent Takeda a Notice of Paragraph IV Certification, in which it informed Takeda that it had submitted an Abbreviated New Drug Application ("ANDA") regarding the sale of pioglitazone before the expiration of certain patents ("September 8 Notice"). That notice described Mylan's belief that the '777 patent was invalid on the basis of obviousness due to Compound 16 of U.S. Patent No. 4,287,200 (the " '200 Patent"), which Mylan asserted is identical to a Compound 14 identified in a prior publication authored by Dr. Sohda (the "Sohda article").[1]

In January of this year, in response to a 30(b)(6) notice from Takeda, Mylan identified three persons as knowledgeable with respect to its claim that the '777 patent is invalid on the basis of obviousness: Dr. John O'Donnell, Mylan's chief scientific officer; Wayne Talton, Mylan's head of regulatory affairs; and Shelly Monteleone, a patent attorney who works at Mylan. Dr. O'Donnell remains unable to testify due to medical reasons, and although both Talton and Mon-

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[1] This publication is Sohda et al., *Studies on Antidiabetic Agents.II. Synthesis of 5-[4-(1-;Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives, Chem.* Pharm. Bull. Vol. 30(10)-3580-3600 (1982).

teleone were deposed, neither one furnished relevant testimony regarding the factual and/or scientific bases for Mylan's Paragraph IV certification.

As a result, on March 17, 2005, Takeda served contention interrogatories on Mylan, in which it requested that Mylan identify "every claim of the Takeda Patents" that Mylan contends is not valid or is unenforceable and that Mylan provide "[a] complete explanation of [its] basis for its contention that each such claim is not valid or is unenforceable." Takeda also served a second 30(b)(6) notice on Mylan on April 13, 2005 that explicitly requested that Mylan produce a witness to testify to "[e]ach and every basis upon which [Mylan] contend[s] or will contend that [the '777 Patent] is invalid, unenforceable, or will not be infringed (whether or not such basis is contained in the Paragraph IV Certification)" as well as to "[e]ach and every fact supporting or undermining" these bases. These two issues constituted Topics 6 and 7 of Takeda's 30(b)(6) notice.

On April 25, Mylan responded to Takeda's contention interrogatories and did not mention any basis for a claim of obviousness with respect to the '777 Patent. Instead, it stated for the first time that the '777 Patent is unenforceable due to Takeda's lack of good faith and candor in applying to the Patent and Trademark Office for that patent.[2] Several days later,

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[2] In relevant part, Mylan's response reads as follows:
Mylan responds that every claim of the '777 patent is unenforceable. The named inventors of the '777 patent and/or one or more other persons under a duty of candor to the PTO made affirmative misrepresentations of material fact, failed to disclose material information and/or submitted false material information in the application which issued as the '777 patent and in the Amendment and Declaration submitted to the PTO on November

on April 29, 2005, Mylan completed its objections to the April 13 30(b)(6) Notice. In these objections, Mylan refused to respond to Topics 6 and 7 on the grounds that the information sought was protected by the attorney-client privilege and work-product immunity and that Takeda instead should seek to discover the bases for Mylan's claims of invalidity or unenforceability of the '777 Patent through contention interrogatories. Subsequently, Takeda and Mylan engaged in unsuccessful negotiations as to the timing of the 30(b)(6) deposition.

Given the parties' inability to agree upon an appropriate time for this deposition, as well as the parties' continuing debate about the scope of that deposition and Dr. O'Donnell's ability to testify, a May 25 telephone conference, which was held on the record, addressed these issues, inter alia.During that conference, it was noted that Mylan had not complied with the Court's prior instructions regarding the scheduling of depositions. The Court further recounted that per the parties' consent, Mylan was required to produce a 30(b)(6) witness and that that witness was required to "have, as part of the preparation for that deposition, a meeting with Dr. O'Donnell to obtain all relevant information necessary to respond *fully and completely* to the 30(b)(6) deposition" notice. (Emphasis added.)[3]

25, 1986, all of which information would have been considered important to the Patent Examiner in deciding whether to allow the application to issue as the '777 patent. Such affirmative misrepresentations, failures to disclose material information and submissions of false material information were done with intent to deceive the Patent Examiner so as to induce the PTO to issue the '777 patent.

[3] The Court also ordered during the May 25 telephone conference that Dr. O'Donnell may not submit "an affidavit in connec-

On June 2 and 3, Takeda deposed Brian Roman ("Roman"), Mylan's designated 30(b)(6) witness. Despite the Court's May 25 Order, Roman did not testify to Topics 6 and 7 during his deposition. Although Roman was asked whether the paragraph IV certification "contain[s] all of the reasons why Mylan contends that the claims of the '777 Patent are invalid or unenforceable of which it was aware on or before September 8, [2003]," counsel for Mylan instructed him not to answer the question. Roman did respond, however, to questions regarding various compounds identified in the Sohda article. When asked whether several compounds, including Compound 57, in the Sohda article would be deemed to be a compound of interest to "one of ordinary skill in the art," Roman explained that "if one were looking for a compound that had an acceptable toxicity profile as well as the types of activity that one's looking for here," the body weight and fat weight increases associated with compounds 57 and 58 "should cause one to rule that out."

On June 6, 2005, three days after Roman's deposition, Mylan served supplemental responses to Takeda's contention interrogatories. In these supplemental responses, Mylan asserted for the first time that the '777 Patent is invalid as obvious on the basis of Compound 57 of the Sohda article, which is equivalent to Compound 40 of the '200 Patent and to which Mylan assigns the shorthand "2-pyridal derivative".[4]

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tion with summary judgment practice or appear[ ] as a trial witness unless he was produced for a deposition" before the May 27, 2005 close of fact discovery.

[4] Mylan asserts that Compound 57 of the Sohda article is the same as that compound "denominated by Takeda as compound 3894."This Opinion refers to this compound as Compound 57.

According to Mylan's supplemental response, "[p]ioglitazone is an obvious modification of the 2-pyridal derivative, which the prior art teaches possesses hypolipidemic and hypoglycemic activities with low toxicity. Pioglitazone is not unexpectedly different in activity or toxicity from the 2-pyridal derivative."[5]

By way of a June 14, 2005 letter, in which it described much of the above history, Takeda argued that Mylan had been "playing a shell game" with respect to its attack on the '777 Patent and requested that this Court enter an Order precluding Mylan from introducing at trial any evidence as to invalidity of the '777 Patent except based on obviousness "as expressly set forth in the Detailed Legal and Factual Basis for Certification which Mylan sent to Takeda on September 8, 2003." A conference in this action was held on that day, during which the parties principally discussed the evidentiary bases for Mylan's motion for leave to amend its answer to assert a claim of inequitable conduct and whether prejudice would result from the granting of the motion. Noting that Mylan had identified two late-disclosed documents, as well as related deposition testimony, that might support an inequitable conduct claim, that motion was granted through a June 15, 2005 Order.

Toward the end of the June 14 conference, however, the Court asked Mylan's counsel to address Takeda's June 14 letter. Counsel stated that he understood "the nature of our allegation on obviousness [to be a]

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[5] In contrast to the detailed analysis contained in its Paragraph IV certification, Mylan's June 6 notification regarding Compound 57 was remarkably vague.

purely legal argument, possibly supplemented with some expert scientific testimony." Counsel further argued that 35 U.S.C. § 282" provides for a deadline some point prior to the trial at which a defendant must identify all prior art to be cited against the patent. Up until that time, not only can you add new arguments and new theories, you can add new references to be asserted against the patent." Takeda's counsel disagreed, contending that the law does not allow an ANDA applicant to change its theory. Given this disagreement, the June 15 Order provided that Mylan's reply to Takeda's June 14 letter was due on June 16, and that Takeda's reply was due on June 17.

In its June 16 letter, Mylan contested Takeda's request for an order of preclusion on several grounds. First, Mylan asserted that where an ANDA applicant attacks a patent claim on the basis of obviousness under 35 U.S.C. § 103, "[e]xpert opinion is relied upon to establish whether a person of ordinary skill in the art to which the patent pertains would have found the invention to be obvious in view of the prior art." Mylan further stated that in pursuing its claim that the '777 claim was invalid, it would "not rely on information or testimony from Mylan or any of its employees" but would instead provide "the detailed bases for Mylan's invalidity arguments" in its expert reports. As a result, it argued, Takeda could not claim to be prejudiced by its June 6 responses.

With respect to whether or not Roman was obligated to testify as to Topics 6 and 7 of Takeda's 30(b)(6) notice, Mylan noted that it had objected to these topics and that Takeda had not addressed them in a letter to the Court. It further noted that Roman could not

have provided testimony regarding Topics 6 and 7 of Takeda's 30(b)(6) notice because prior to June 6, neither Roman nor any other Mylan employee possessed "non-privileged information responsive to [these topics] regarding any of Mylan's invalidity contentions other than those set forth in the Detailed Statement that Mylan provided to Takeda in September, 2003."With respect to Roman's testimony regarding Compound 57, Mylan contended that as Roman is "not a person of ordinary skill in the art to which [the '777 Patent] pertains," his statements about such prior art were irrelevant to this action. Finally, Mylan's June 16 response cited only one case, *Smithkline Beecham Corp. v. Apotex Corp.*, No. 98 C 3952, 2000 WL 116082 (N.D.Ill. Jan. 24, 2000), which it stated stood for the proposition that it should not be held to the theories set forth in a notice letter.

It is unnecessary on this motion to summarize Takeda's June 17 reply, which primarily disputed Mylan's reading of *Smithkline Beecham* and argued that Mylan's changing its theory of obviousness would exert "palpable" prejudice on Takeda, in any detail. It should be noted, however, that like Mylan, Takeda relied on little case law in its letter briefs on this issue. Takeda's June 14 letter contained no case law, and aside from discussing *Smithkline Beecham*, Takeda's June 17 letter presented only one other case, *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed.Cir.1998).

Discussion

Local Civil Rule 6.3 reads in pertinent part as follows:

A notice of motion for reconsideration or reargument

shall be served within ten (10) days after the docketing of the court's determination of the original motion. There shall be served with the notice a memorandum setting forth concisely the matters or controlling decisions which counsel believes the court has overlooked.

S.D.N.Y. Local Civil Rule 6.3. In moving for reconsideration, the moving party "must demonstrate that the court overlooked controlling decisions or factual matters that were put before it on the underlying motion." *Eisemann v. Greene*, 204 F.3d 393, 395 n .2 (2d Cir.2000) (citation omitted). In addition, the moving party may not "advance new facts, issues, or arguments not previously presented to the Court." *Geneva Pharm. Tech. Corp. v. Barr Labs.*, Inc., No. 98 Civ. 3607(RWS), 2002 WL 1933881, at *1 (S.D.N.Y. Aug. 21, 2002) (citation omitted).

Courts narrowly construe Local Civil Rule 6.3 and apply it strictly against the moving party "so as to avoid repetitive arguments on the issues that have been considered fully by the court" and "to prevent the practice of a losing party examining a decision and then plugging the gaps of a lost motion with additional matters." *Mones v. Commercial Bank of Kuwait*, No. 18 Misc. 302(SAS), 2005 WL 1963955 (S.D.N.Y. Aug. 11, 2005), at *2 (citation omitted). The decision to grant or deny the motion is within the sound discretion of the district court. See *Devlin v. Transp. Communications Int'l Union*, 175 F.3d 121, 132 (2d Cir.1999).

Mylan contends that the June 21 Order overlooked the fact that Mylan "could not possibly have devel-

oped" its obviousness defense based on Compound 57 "until after Takeda's belated production of critical comparative data." Mylan asserts that "the evidence of similar activity and toxicity upon which Mylan's [obviousness] defense is based are derived solely from data in Takeda's document production" that Mylan did not receive in unredacted form until February, March, and April 2005. This argument is entirely unavailing. At no point during the June 14 conference or in its June 16 letter did Mylan discuss any of the evidentiary bases for its obviousness defense with respect to the '777 Patent, much less contend that Takeda's delay in producing unredacted versions of any documents was the reason that Mylan waited until June 6 to assert such a defense.[6]

Yet even if Mylan had presented these facts in opposing Takeda's request, Mylan's argument is fundamentally flawed. At the June 14 conference, in the context of justifying Mylan's delay in asserting its inequitable conduct claim, counsel for Mylan represented that although compound 3894 was "expressly identified" in a prior art publication, it was not until receiving the unredacted version of an internal Takeda report labeled A-15-34 on February 4, 2005 that

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[6] To the extent Mylan seeks to explain this omission by reference to the fact that letters to the Court are subject to a two-page limit, that explanation can be swiftly rejected. As the parties to this litigation well know, whenever their correspondence indicates that further explication of an issue is necessary, the Court schedules conferences or permits briefing to give them an opportunity to develop their argument. One such conference was held on June 14, and the June 16 letter could have alluded easily to the discussion at the June 14 conference of the unredacted documents if that were helpful to explain Mylan's tardy disclosure of the new theory of obviousness.

Mylan understood that Takeda failed to report to the PTO that its internal research demonstrated that "pioglitazone was not so superior" to this compound. Mylan's counsel further stated that Takeda's production of this data "would have led the examiner to understand that you can't patent pioglitazone because it's not different than what was in the prior art." Yet even accepting that Mylan did not obtain an unredacted version of A-15-34 until February 2005, a patentee's internal data is irrelevant to a claim of invalidity on the basis of obviousness. As the Federal Circuit has explained, and as Takeda points out in its opposition brief, an invention is obvious when a person of ordinary skill in the prior art would have expected a particular result given the "knowledge *already available* in the art at the time" of the patentee's invention. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096 (Fed.Cir.1986) (emphasis supplied).

In its reply, Mylan does not contest Takeda's description of the law of obviousness. Nor does Mylan challenge Takeda's assertions that Mylan has had all of the pertinent prior art in its possession for at least two years and that Mylan has had "all" of the Compound 57 test data relied on by Mylan's expert in his recently produced expert report since the summer of 2004. Instead, Mylan shifts its argument and now claims that it could not have asserted that the '777 Patent is obvious on the basis of Compound 57 until "completing discovery on all bases on which Takeda might argue the unexpected superiority of pioglitazone over [Compound 57]." Mylan further argues that given that patent holders may introduce into evidence any "work done in studying the invention," even if not included in the patent application, in re-

sponse to a litigation attack on the patent's validity, *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004), its own prolonged investigation was "perfectly appropriate." That the law allows patent holders to respond to attacks on a patent's validity by using data not in the prior art has no bearing on what showing Mylan must make to prove invalidity on the basis of obviousness in the first instance and is therefore beside the point.

Mylan next argues that the June 21 Order improperly relied on certain facts regarding Roman's deposition. Specifically, Mylan deems erroneous that portion of the Order that notes that Mylan's counsel's objected to questions "as to the basis for Mylan's contentions that the '777 Patent is invalid, unenforceable, or not infringed, other than those disclosed in the September 8 Notice" on the basis of the attorney-client and work-product privileges. According to Mylan, its counsel's objections were proper as Mylan not only "made clear in advance of the deposition" that it would not produce a fact witness on Topics 6 and 7, but also because Mylan would have violated the protective order in this case had it shared with Roman the highly-confidential "activity and toxicity data" upon which Mylan's claim of obviousness based on Compound 57 hinges. Since a claim of obviousness must be based on publicly available knowledge, Mylan's contention that it would have violated a protective order to respond to this question is specious. In any event, the description of Roman's deposition is ancillary to the analysis underlying the June 21 Order.

Finally, Mylan argues that the June 21 Order incor-

rectly applied *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed.Cir.1999), by failing to consider carefully whether Takeda has been prejudiced by Mylan's belated disclosure of its defense that the '777 Patent is obvious on the basis of Compound 57. In *Lydall*, the Federal Circuit examined whether the district court appropriately exercised its discretion to preclude the defendant from relying on a prior art reference first disclosed to the plaintiff three months after the close of discovery. Although the plaintiff argued that pursuant to 35 U.S.C. § 282, a party may disclose the prior art upon which it relies for an assertion of invalidity on the basis of obviousness until thirty days prior to trial, the *Lydall* court disagreed, holding that where "a specific judicial directive for the timing of discovery" has been set, that procedure, and not 35 U.S.C. § 282, "necessarily governs that trial" and "establishes the procedure to which the parties are bound."Id. at 551.In so holding, the *Lydall* court noted that the purpose of both Section 282 and the Federal Rules of Civil Procedure is "to prevent unfair and prejudicial surprise, not to facilitate last-minute production of evidence."Id. Nevertheless, at no point does *Lydall* require a district court to make a finding of prejudice in order to preclude a theory not made available to the other side during the discovery period.

Even if *Lydall* compels a district court to find that the party seeking preclusion has been prejudiced, Mylan's claim that Takeda will suffer no prejudice by virtue of its change in theories is wrong. According to Mylan's June 16 letter, Takeda will not be surprised at trial because Mylan will disclose "the bases for Mylan's invalidity theories" during expert discovery. Al-

lowing Mylan to assert a new theory of obviousness, based on Compound 57, and to elaborate upon this theory through expert discovery will require an alteration of the expert discovery schedule. In addition, Takeda would be entitled to reopen fact discovery to investigate why Mylan believes that the '777 Patent is obvious in light of Compound 57. As Roman's deposition testimony demonstrates, appropriate questioning in fact discovery can undermine Mylan's obviousness theory. Especially given that the parties have been repeatedly warned that their January 2006 trial date is firm, requiring Takeda to revisit its expert and fact discovery in order to give it a fair opportunity to respond to Mylan's newly asserted theory would result in "palpable" prejudice to Takeda. For all of the above reasons, Mylan's motion for reconsideration of the June 21 Order is denied.

Conclusion

Mylan's motion for reconsideration of the June 21 Order precluding Mylan from introducing at trial "any evidence as to the invalidity of the '777 Patent except based on a theory of obviousness set forth in the September 8 Notice" is denied.

SO ORDERED:

S.D.N.Y.,2005.

Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.

Not Reported in F.Supp.2d, 2005 WL 2092920 (S.D.N.Y.)

United States District Court,
S.D. New York.
TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals, North America, Inc.,
Plaintiffs,
v.
MYLAN LABORATORIES, INC. and UDL Laboratories, Inc., Defendants.
No. 03 Civ. 8253(DLC).
June 15, 2005.

MEMORANDUM OPINION AND ORDER
COTE, J.

On September 8, 2003, defendant Mylan Laboratories, Inc. ("Mylan") sent a Notice of Paragraph IV certification to plaintiff Takeda Chemical Industries, Ltd. ("Takeda"), in which it informed Takeda that it had submitted an ANDA regarding the sale of pioglitazone before the expiration of certain patents ("September 8 Notice"). In that notice, Mylan described its belief that U.S. Patent No. 4,687,777 (the "'777 Patent") was invalid on the basis of obviousness due to Compound 16 of U.S. Patent No. 4,287,200 (the " '200 Patent"). Mylan asserted that Compound 16 of the '200 Patent is identical to a Compound 14 identified in a prior publication of Dr. Sohda.

On March 17, 2005, Takeda served contention interrogatories on Mylan, in which Takeda requested that Mylan detail its contentions as to the invalidity of the '777 Patent. Mylan's response of April 25, 2005 did not touch upon the obviousness of the '777 Patent. Instead, Mylan contended that the '777 Patent was unenforceable on the basis that Takeda had breached

its duty of good faith and candor in applying to the PTO for the '777 Patent. Additionally, on June 2 and 3, 2005, Takeda deposed a representative of Mylan pursuant to Rule 30(b)(6), Fed.R.Civ.P. At that deposition, Takeda inquired as to the bases for Mylan's contentions that the '777 Patent is invalid, unenforceable, or not infringed, other than those disclosed in the September 8 Notice. At several points, Mylan's counsel objected to this line of questioning, citing the attorney-client and work product privileges. After the close of fact discovery, on June 6, 2005, Mylan served supplemental responses to Takeda's interrogatories, in which it expresses that the '777 Patent is invalid on the basis of obviousness due to a previously unmentioned compound, Compound 57, as described in the Sohda publication.

On June 14, Takeda wrote a letter seeking an order precluding Mylan from introducing at trial any evidence as to invalidity of the '777 Patent except based on obviousness as set forth in the September 8 Notice. Pursuant to a June 15 Order, the parties submitted additional correspondence concerning this issue. In its submission, Mylan emphasizes *Smithkline Beecham Corp. v. Apotex Corp.*, No. 98 C 3952, 2000 WL 116082 (N.D.Ill. Jan. 24, 2000), which it cites for the proposition that there is "no authority for limiting [a defendant] to the theories set forth i[n] their notice letter."

Mylan misunderstands the law. Although as a general matter an ANDA applicant may be able to assert theories other than those outlined in a notification letter, "when the court has set and the parties have agreed to a discovery period, that procedure necessar-

ily governs the trial.... [A] specific judicial directive for the timing of discovery establishes the procedures to which the parties are bound." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 551 (Fed.Cir.1998). During the period of fact discovery, Mylan never articulated any basis for the invalidity of the '777 Patent on the ground of obviousness other than Compound 14 of the Sohda publication. Therefore, it is hereby

ORDERED that Mylan may not offer at trial any evidence as to invalidity of the '777 Patent except based on a theory of obviousness set forth in the September 8 Notice.

SO ORDERED:
S.D.N.Y.,2005.
Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT
2007-1269, -1270

TAKEDA CHEMICAL INDUSTRIES, LTD., and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,
Plaintiffs-Appellees,
v.
MYLAN LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., and UDL LABORATORIES, INC.,
Defendants-Appellants.
and
ALPHAPHARM PTY. LTD. and GENPHARM, INC.,
Defendant-Appellants.

Appeal from the United States District Court for the Southern District of New York in Case no. 03-CV-8253 and 04-CV-1966, Judge Denise L. Cote.

ORDER

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ORDER

A petition for rehearing en banc having been filed by the Appellants,* and the matter having first been

* Petition filed by Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc.

referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on January 30, 2009.

FOR THE COURT,
Jan Horbaly
Clerk

Dated: 01/23/2009

cc: William A. Rakoczy, Edgar H. Haug,
David G. Conlin,
Thomas C. Goldstein J

JAN 23, 2009
IAN HORBALY CLERK
TAKEDA CHEMICAL Y MYLAN LABS, 2007-1269,-1270
(DCT -03-CY-8253)

Amicus Curiae, Generic Pharmaceutical Association was granted leave to file a brief in support of the Appellants' petition for rehearing en banc.

21 USC CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT

01/03/2007

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)

(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)

(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagr. ph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of

section 321 (p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant

and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed.—

(i) Agreement to give notice.— An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice.— An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph—

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice.— An applicant required under this subparagraph to give notice shall give notice to—

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice.— A notice required under this subparagraph shall—

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary

seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)

(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)

(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applica-

tions.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division

shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.
(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.
(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).
(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—
(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;
(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;
(C)
(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;
(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug,

or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321 (p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)

(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not

the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that

(i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or

(ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for

grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)

(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval

shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) of this section before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed—

(aa) if the judgment of the district court is appealed, the approval shall be made effective on—

(AA) the date on which the court of appeals decides

that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271 (e)(4)(A) of title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period.—

(I) Effectiveness of application.— Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the applica-

tion shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions.— In this paragraph:

(aa) 180-day exclusivity period.— The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) First applicant.— As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application.— As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval.—

(AA) In general.— The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation.— A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(C) Civil action to obtain patent certainty.—

(i) Declaratory judgment absent infringement action.—

(I) In general.— No action may be brought under section 2201 of title 28 by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action.— If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will

not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application.— For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose,

and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action.—

(I) In general.— If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action.— Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages.— An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period.—

(i) Definition of forfeiture event.— In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market.— The first applicant fails to market the drug by the later of—

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section.

(II) Withdrawal of application.— The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application

does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification.— The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval.— The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner.— The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of title 15, except that the term includes section 45 of title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents.— All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture.— The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant.— If all first applicants forfeit the 180-day exclusivity period under clause (ii)—

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)

(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsec-

tion which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is

approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection

(b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)

(A)

(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, which-ever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.
(8) For purposes of this subsection:
(A)
(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.
(B) A drug shall be considered to be bio-equivalent to a listed drug if—
(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.
(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish al-

ternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of—

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section.

Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(l) Public disclosure of safety and effectiveness data

Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown—

(1) if no work is being or will be undertaken to have the application approved,

(2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(3) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(4) if the Secretary has determined that such drug is not a new drug, or

(5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the

approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.
(m) "Patent" defined
For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.
(n) Scientific advisory panels
(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.
(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.
(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—
(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;
(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;
(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be

brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member's own scientific work is involved.

(5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its

business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS–15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, for persons in the Government service employed intermittently.

(7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

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01/03/2007

(e)

(1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

(2) It shall be an act of infringement to submit—

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent, or

(B) an application under section 512 of such Act or under the Act of March 4, 1913 (21 U.S.C. 151–158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent,

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of

which is claimed in a patent before the expiration of such patent.

(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under paragraph (1).

(4) For an act of infringement described in paragraph (2)—

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product, and

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product.

The remedies prescribed by subparagraphs (A), (B), and (C) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285.

(5) Where a person has filed an application described in paragraph (2) that includes a certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and neither the owner of the patent that

is the subject of the certification nor the holder of the approved application under subsection (b) of such section for the drug that is claimed by the patent or a use of which is claimed by the patent brought an action for infringement of such patent before the expiration of 45 days after the date on which the notice given under subsection (b)(3) or (j)(2)(B) of such section was received, the courts of the United States shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under section 2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.

(f)

(1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.

(h) As used in this section, the term "whoever" includes any State, any instrumentality of a State, and any officer or employee of a State or instrumentality of a State acting in his official capacity. Any State, and any such instrumentality, officer, or employee, shall be subject to the provisions of this title in the same manner and to the same extent as any nongovernmental entity.

(i) As used in this section, an "offer for sale" or an "offer to sell" by a person other than the patentee, or any designee of the patentee, is that in which the sale will occur before the expiration of the term of the patent.

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Notice of certification of invalidity or noninfringement of a patent.

(c) Contents of a notice. In the notice, the applicant shall cite section 505(j)(2)(B)(ii) of the act and shall include, but not be limited to, the following information:

(1) A statement that FDA has received an abbreviated new drug application submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The abbreviated application number.

(3) The established name, if any, as defined in section 502(e)(3) of the act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant shall include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.